THE American Journal OF Gastroenterology

VOL. 33, NO. 4 APRIL, 1960

Gastrointestinal Bleeding in Hereditary Hemorrhagic Telangiectasia

Clinical Evaluation of the Gastrointestinal Tract in the Aged

The Corticosteroid-Induced Peptic Ulcer

The Ominous Reciprocity Between Liver Disease and Pancreatitis

Further Experiences with Hemagglutination in Viral Hepatitis

A Comparative Study of Hydrochlorothiazide and Chlorothiazide of Blood Ammonia and Electrolyte Imbalance in Cirrhotic Patients

Twenty-fifth Annual Convention
Philadelphia, Pennsylvania
23, 24, 25, 26 October 1960

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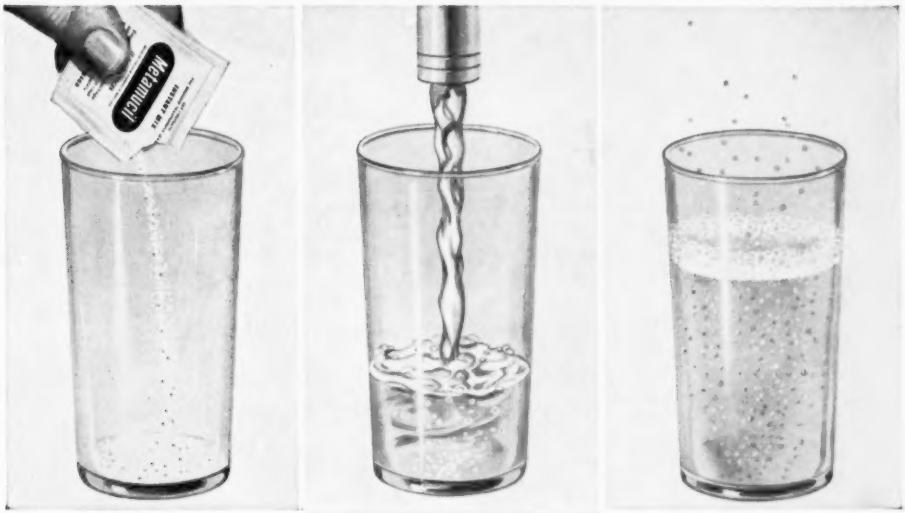

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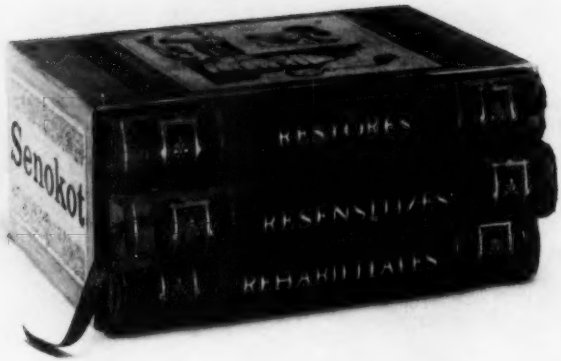

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THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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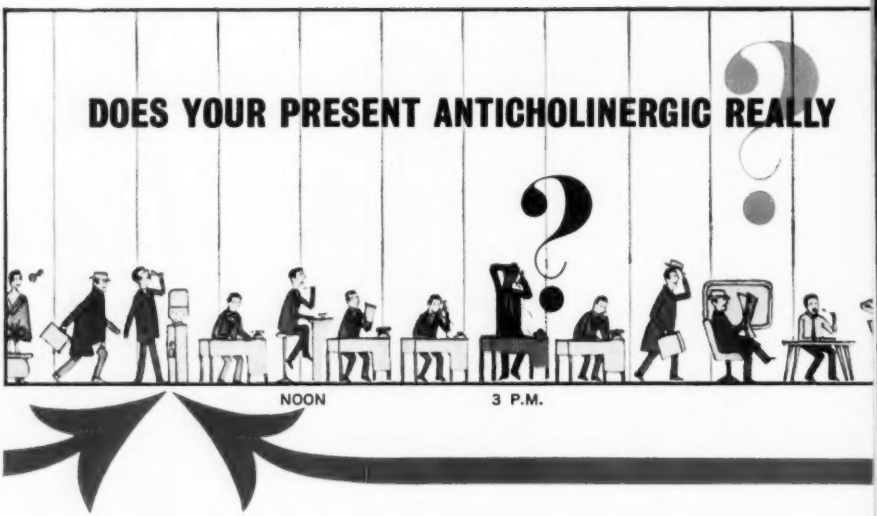

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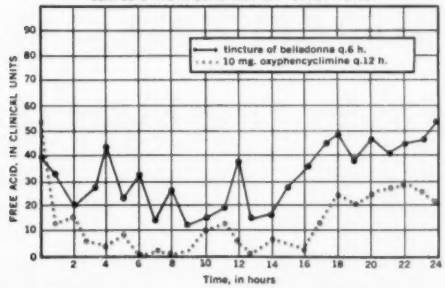

Clinical Diagnosis: Peptic Ulcer—Gastritis—Gastroenteritis—Colitis—Functional Bowel Syndrome—Duodenitis—Hiatus Hernia (symptomatic)—Irritable Bowel Syndrome—Pylorospasm—Cardiospasm—Biliary Tract Dysfunctions—and Dysmenorrhea.

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References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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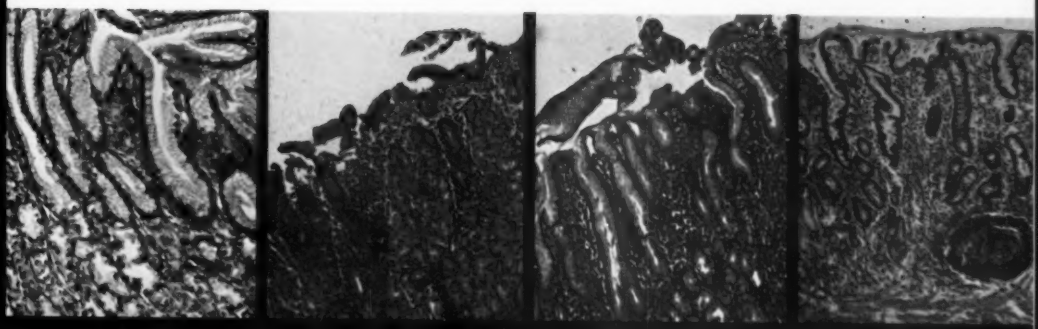
1. Breidenbach, L., and Secor, S. M.: Proper Handling of the Colostomy Patient, Amer. J. Surg. 93:50, 1957.

GASTRITIS

a pathological entity

histologically demonstrable



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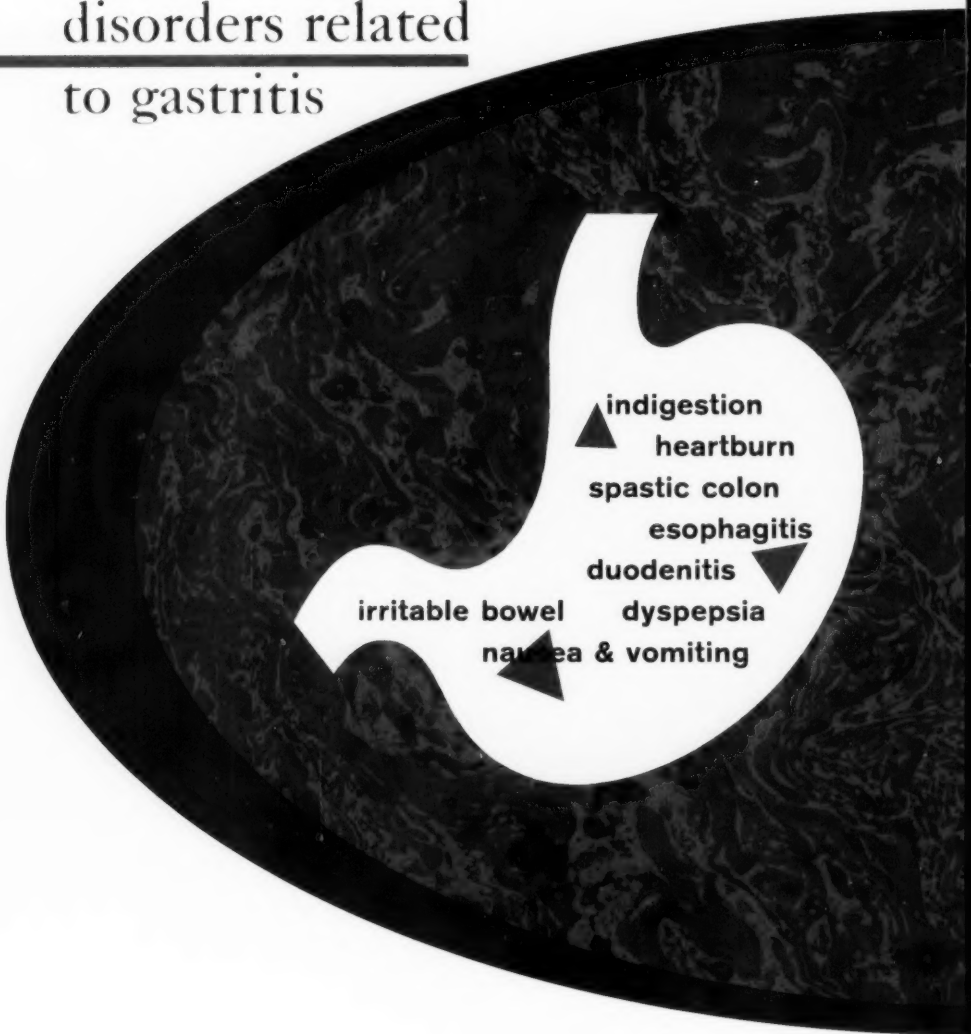
Microscopic views of gastric biopsies, courtesy of E. Deutsch, M.D., originally published as part of study, Chronic Gastritis, Deutsch, E., and Christian, H. J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

disorders related to gastritis



symptoms

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Persistent, generalized upper abdominal pain—as opposed to localized pain of peptic ulcer

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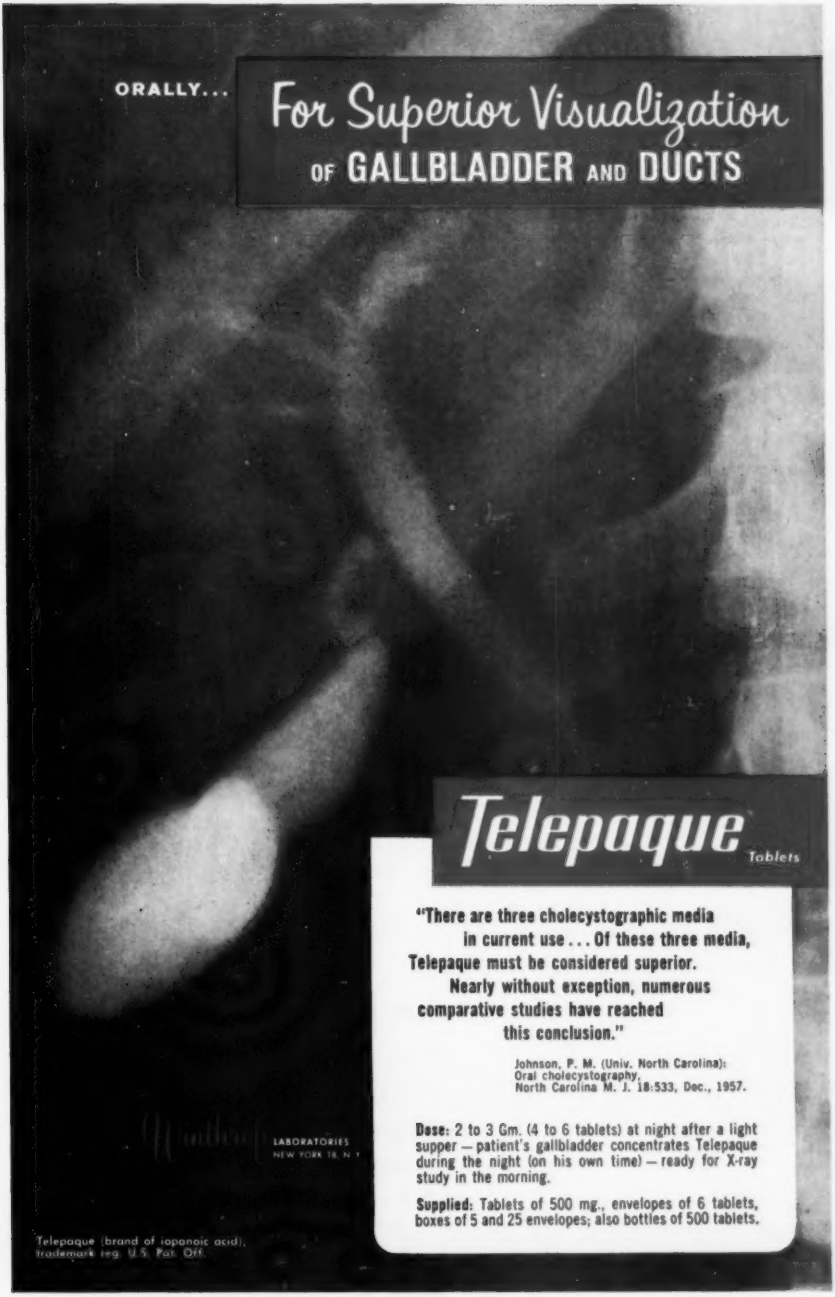
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Johnson, P. M. (Univ. North Carolina): Oral cholecystography, North Carolina M. J. 18:533, Dec., 1957.
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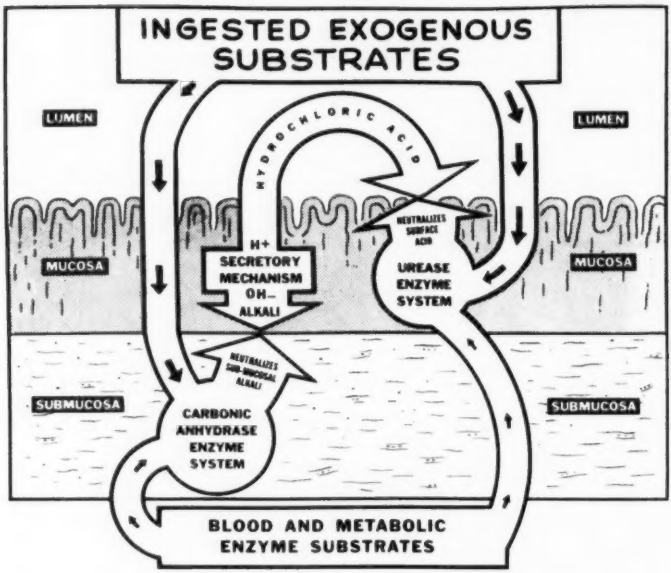

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*Goodfriend, Vanderkleed & Goodfriend. "Enzymatic Therapy of Peptic Ulcer and Digestive Disorders." American Journal Gastroenterology, Vol. 33, No. 1, Pgs. 80-89, January 1960.

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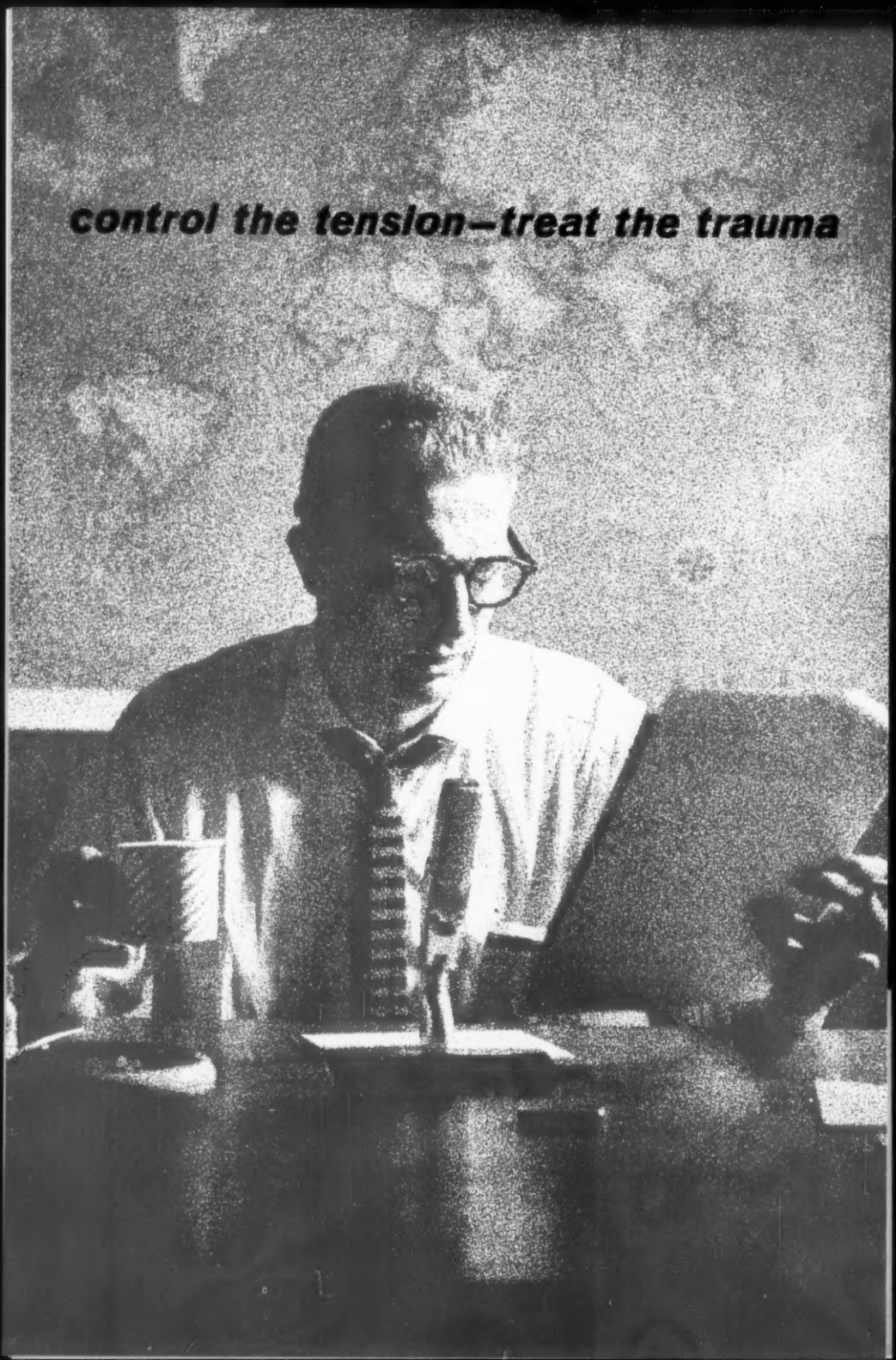
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Adjust to patient response.

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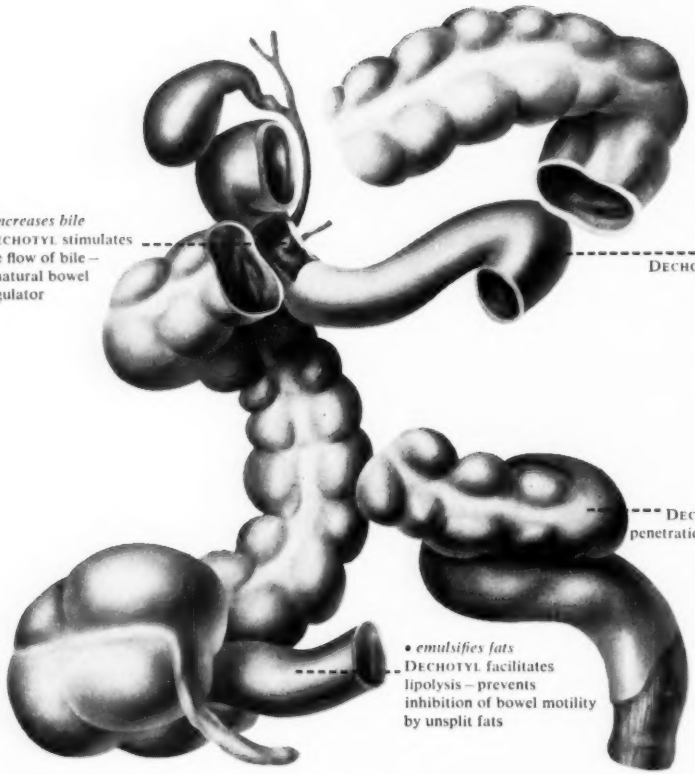
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THE American Journal OF Gastroenterology

A monthly journal of Gastroenterology, Proctology and Allied Subjects
FORMERLY THE REVIEW OF GASTROENTEROLOGY

VOLUME 33 APRIL, 1960 NUMBER 4

GASTROINTESTINAL BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA*

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH MASSIVE RECURRENT HEMORRHAGE NECESSITATING RIGHT COLECTOMY

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DEFINITION AND INTRODUCTION

Hereditary hemorrhagic telangiectasia (hereditary epistaxis, hereditary angiomata, familial telangiectasia or Rendu-Osler-Weber disease) is a hereditary vascular anomaly causing hemorrhage from the capillaries and venules of the skin and mucous membranes. This disease is rarely considered in unexplained cases of gastrointestinal bleeding. Peptic ulcer is often suspected, and rarely can the two conditions coexist[1].

We hope with our case reports and brief review of the literature to alert the gastroenterologists and surgeons to consider the remote possibility of hereditary hemorrhagic telangiectasia in the differential diagnosis of otherwise unexplained gastrointestinal hemorrhage.

Case 1:—Mrs. J. T., 84 years of age, was referred to our service on 10 December 1958, by her physician. She had been essentially well until February,

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.

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1958, when a sudden episode of severe melena required two transfusions. The acute blood loss precipitated an acute myocardial infarction and congestive heart failure. Since that admission, the patient had ten episodes of massive rectal bleeding requiring transfusions for relief. Repeated hospitalizations for bleeding occurred in July, twice in November and twice in December in her local hospital. Five transfusions were necessary prior to her immediate transfer to Santa Barbara. Since February of 1958, her local physician had done three complete upper and lower gastrointestinal x-ray series, interval studies of the small bowel, several sigmoidoscopic examinations and a complete special hemorrhagic study which was normal. A small hiatus hernia was the only x-ray finding.

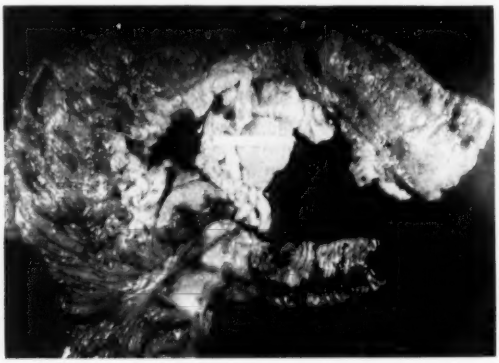

Fig. 1—Case 1, terminal 6 cm. of ileal mucosa and mucosa on both sides of ileocecal valve show discrete elevated telangiectasias (surgical specimen).

Family history:—Her mother and father died in their 80's of natural causes and had had no hemorrhages. A sister, age 77, had had no bleeding; but a brother had had repeated epistaxis and died "young".

The patient had had no previous gastrointestinal bleeding but had repeated epistaxis years ago. It is interesting that 20 years ago with a normal blood pressure she had a so-called "brain hemorrhage" and was hospitalized for five weeks.

Physical examination revealed a profuse, liquid, red discharge from the rectum, 600 c.c. being lost on admission. The skin showed multiple spider telangiectasias of the cheeks, ruddy complexion and several nodular angiomas on the lips. Several angiomas were seen at the base of the tongue and inside lips. Careful examination of the ears, fingertips and feet showed no more lesions. Aortic stenosis and cardiac enlargement were evident. Liver and spleen were not enlarged.

Admission hemoglobin was 9.6 gm., red blood count 3,170,000; and all bleeding and clotting times, platelet counts, prothrombin times and Rumpel-Leede test were normal. Electrocardiogram showed first degree heart block and old anterior and posterior myocardial infarction.

Massive rectal bleeding continued, and in spite of transfusions the hemoglobin dropped to 7 gm. and red blood cells to 2,300,000 in 48 hours. Gastric aspiration with Ewald tube was negative for blood. This latter determination helped us in localizing the bleeding below the ligament of Treitz.

On 11 December she continued downhill with massive rectal bleeding. Exploratory laparotomy was carried out as an emergency procedure. The right colon contained considerable blood as did the distal six inches of ileum. Above this point no evidence of bleeding was apparent from serosal examination. There

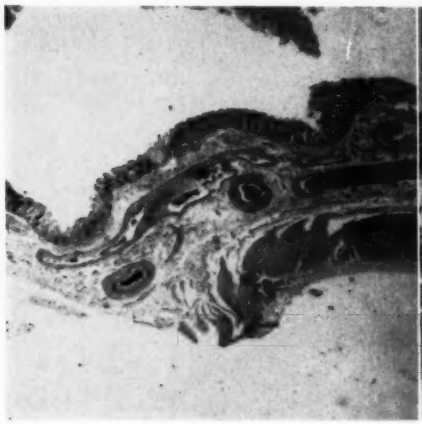

Fig. 2

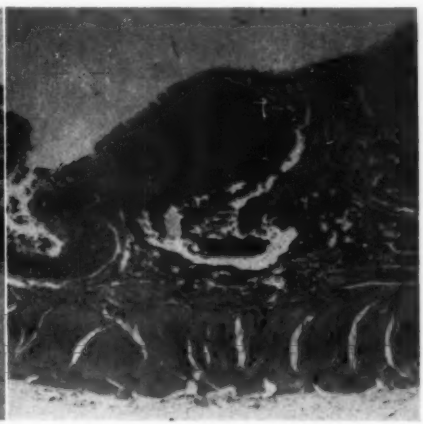

Fig. 3

Fig. 2—Case 1, vessels of submucosa of terminal ileum reveal increase in number of vessels and capillaries.

Fig. 3—Case 1, vessels of submucosa of terminal ileum, thin-walled and dilated with bleeding.

were several 1-2 mm. serosal telangiectasias in the distal ileum. The right colon was opened, its contents aspirated and the mucous membrane examined. A rosette of punctate, actively bleeding telangiectasias were scattered through the ileocecal valve and in the cecum. Sigmoidoscope was then passed through the ileocecal valve proximally for three feet, and no mucosal abnormalities were seen. It was then passed distally to the splenic flexure, and no further abnormalities were seen. Surgery included colotomy, proximal and distal proctoscopic examination, right colectomy and ileotransverse colostomy.

Gross pathology:—No subserosal telangiectasias are evident. The terminal 6 cm. of ileal mucosa contains discrete, slightly elevated, bright red to dark red

telangiectasias from 0.5-1 mm. in diameter. The mucosa on both sides of the ileocecal valve contains numerous discrete and confluent bright red areas measuring up to 3 mm. in diameter. In the region of the hepatic flexure and transverse colon, the mucosa contains bright red areas 2-3.5 cm. in diameter.

Microscopic description:—Vessels of the submucosa of the terminal ileum reveal increase in the number of vessels and capillaries. Many are thin-walled and dilated. The cecum and colon show similar changes.

Microscopic diagnosis:—Compatible with hereditary hemorrhagic telangiectasia.

The patient made an uneventful recovery and has had no recurrence of gastrointestinal bleeding to date.

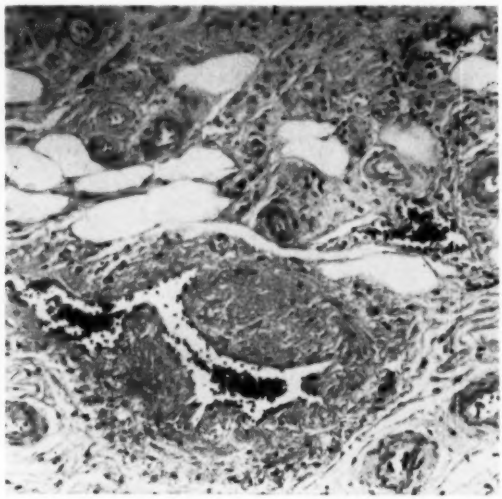

Fig. 4—Case 1, marked increase in number of vessels and capillaries submucosa.

Case 2:—Mrs. B. E., a 39-year old nervous housewife, was referred by her local physician for exploratory laparotomy to exclude an abdominal aneurysm and pancreatic neoplasm. The patient was advised not to have exploratory surgery as our findings were negative, but she insisted.

Family history was negative for bleeding. A brother died of chronic nephritis, and nine siblings were living and well. The patient had a negative history for hemorrhage.

Physical examination showed tiny nodular pinpoint angiomas on the upper lip only. Laparotomy was essentially negative except for numerous 1-2 mm. blue-black subserosal telangiectasias throughout the small bowel.

The patient has made an excellent recovery and her "iatrogenic abdominal disease" has disappeared. We have informed the family of the diagnosis of hereditary hemorrhagic telangiectasia, its prognosis and possible hemorrhagic symptoms in the future.

History

Hereditary hemorrhagic telangiectasia was first described in 1864 by Sutton[2]. Legg[3] in 1876 reported a 76-year old male with repeated nosebleeds and cutaneous nevi, and erroneously called it hemophilia.

We are indebted to Osler in 1901[4] and 1908[5] for the initial complete description. He reviewed Chiari's case of 1887 and Rendu's of 1896. An Osler case displayed gastric telangiectasias at autopsy. In 1907 Parkes-Weber[6] emphasized

Fig. 5—Case 2, nodular and pinpoint facial telangiectasias.

that both sexes are jointly affected and that either transmit the disease. Hanes[7] in 1909 suggested the diagnostic triad of family history, repeated bleeding and multiple telangiectasias. Weber in 1924[8] mentioned the coexisting visceral telangiectasias causing hemoptysis, hematuria or gastrointestinal bleeding. Harper[9] in 1928 found recurrent melena; and Boston[10] in 1930 described three patients with repeated hematemesis, all with mucous membrane telangiectasia. A nevus was found on the gallbladder peritoneum in the first case with two bleeding telangiectasias on the cardia. He ligated the local arteries, and there was no recurrence for five years. His second case showed erosions overlying the coronary vein at autopsy.

In 1931 Fitz-Hugh[11] reported a patient with epistaxis at 25, cutaneous lesions at 40, splenomegaly at 50 and melena at 60. Bronchoscopy and sigmoidoscopy showed telangiectasias. The lesions all regressed at necropsy, suggesting that visceral telangiectasias disappear.

Hurst and Plummer[12] reported three patients out of 17 cases with rectal telangiectasias with sigmoidoscopy as did Meiklo in 1933[13], the latter case with rectal bleeding. Schuster's[14] case had no gastrointestinal complaints but displayed telangiectasias in the stomach and duodenum at autopsy.

In 1939 Renshaw[15], a predecessor of the senior author at the Cleveland Clinic, gastroscoped a patient with hereditary hemorrhagic telangiectasia with unexplained melena, finding 20 millet-seed gastric telangiectasias. He reported the first case of hereditary hemorrhagic telangiectasia described gastroscopically. Proctoscopic examination was normal.

In 1941 Griggs and Baker[16] reported three patients with recurrent melena; and in 1944 Wolfsohn[17] again demonstrated gastroscopically proven telangiectasias as did Rundles[18], the latter case with melena. Gambill[19] of the Mayo Clinic described a woman of 49 with repeated gastric intestinal bleeding. In 1946 Kushlan[20] reviewed the whole problem of gastrointestinal hemorrhage, his case showing melena and gastric telangiectasias, the latter oozing blood gastroscopically. Bell's[21] case had recurrent gastrointestinal bleeding, laparotomy showing telangiectasias on the small intestine serosa. Although this patient did not have visible skin lesions, it was classed as hereditary hemorhagic telangiectasia. Williams'[22] patient had melena, negative gastroscopic and sigmoidoscopic examinations; but surgery showed telangiectasias on the serosa of the small bowel.

Rumball[23], Goldman, Asher and Ware[24] added cases with gastroscopically proven telangiectasias.

In 1953 Shepherd's patient had jejunal telangiectasias with carcinoma of the stomach. Another case had associated duodenal ulcer and gastroscopic telangiectasias.

In 1955 Williams and Brick[25] performed total gastrectomy for a patient with gastric telangiectasias with recurrent hematemesis and melena for cure.

In 1958[26] Vaughn presented a case lacking epistaxis and lacking a familial or hereditary history, but gastrostomy showed telangiectasia as the cause of hematemesis and melena.

Incidence

Hereditary hemorrhagic telangiectasia is uncommon but is being diagnosed more frequently as physicians are aware of it. Garland and Anning[30] reported 20 families in 1950 adding to the 244 families previously reported. In 218 families, 1,451 people were affected. In the Mayo Clinic from 1920 to 1944, 31 cases of Osler-Rendu disease were reported—none with gastrointestinal hemorrhage[19]. Some published reports are merely suggestive and do not withstand sharp evaluation. Shepherd[1] says that British doctors have shown a remarkably negative interest in angiomatous lesions of the gastrointestinal tract. The *British Journal of Surgery* recorded only two examples of the latter (1948 and 1952).

Etiology

Hereditary hemorrhagic telangiectasia is usually prefixed as familial, hereditary or congenital. Each sex can be affected by the disease, and either sex may transmit it. It is developmental, invariably hereditary and mendelian dominant[1]. It is transmitted as a simple dominant factor, not sex-linked, thereby affecting both sexes.

Not every patient, however, has a direct familial or inherited background, and it can bypass generations before returning. The absence of a family history does not cast serious doubt on the diagnosis[35]. There are some patients with characteristic telangiectasia who do not have a family history. Fitz-Hugh[28] explains this on the basis of atavism, skipping a generation. The condition may be so mild that there may be no bleeding tendency, and thus cases are overlooked[35]. Occasionally a mutation occurs or all lesions are internal[36].

Goldstein[37] reported isolated nonhereditary cases. Steiner's[38] first two families showed atavism. The history of his first family shows two examples of atavistic transmission (one by a female and one by a male), neither of whom showed signs of the disease but transmitting it to their respective offspring.

Symptomatology

Usually, soon after adolescence nosebleeds occur. After the second decade, multiple telangiectasias appear on the mucous membranes of the tongue, lips and skin of the ears, fingers and face. Subungual lesions may be diagnostic[6]. The telangiectasias increase in number with age[26], visceral lesions affecting the middle aged and elderly. The most common sites of bleeding are the tongue, lips, hands, nose, buccal mucosa, ears, scalp, gastrointestinal tract, bladder, liver, kidneys, and trachea. Bird's and Jaques'[27] case had multiple telangiectasias in the tongue, cardiac muscle, liver, pancreas, gastrointestinal tract, lungs, adrenal glands, testes and brain.

Boston[10] found telangiectasias enlarging and bleeding more easily after age 40, bleeding rarely occurring before age 10. Occasionally pulmonary A-V aneurysms have been found with hereditary telangiectasia[39]. Clinical bleeding seems to depend more on fate or accessibility of an organ to trauma rather than on a predilection for a certain system[27].

Sturges[35] says there may be a palpable spleen and liver in association with a chronic hypochromic anemia from repeated hemorrhage.

Laboratory Examination

A moderate reduction in red blood cells and reduced hemoglobin may be in evidence with recent bleeding. Also from hemorrhage the platelets and polymorphonuclears may be elevated. All hemorrhagic studies are normal, including bleeding and clotting times and prothrombin time; and there is never a reduc-

tion in platelets. Wells[40], however, reported four cases with positive Rumpel-Leede tourniquet tests and two with prolonged bleeding time; but this is rare.

Character of the Lesions

The telangiectasias commonly seen are of three types:

1. *Pinpoint lesions*, which are most commonly present on the lips, face and hands, are relatively inconspicuous and often totally overlooked at first glance. These small telangiectasias fade partially on firm pressure[36] and should be observed with a glass slide through which color can be observed.

2. *Stellate angiomas*[1], similar to cirrhosis of liver lesions[35], consisting of a punctiform central area flat or raised, from which radiate easily visible vessels. They, too, are bluish or red in color, fade partially on pressure; and pulsation is difficult to reproduce. They are seen particularly on mucosal surfaces of the lips, tongue, nose, cheeks, eyelids and fingers.

3. *Nodular angiomas*, which do not fade at death and so, unlike the delicate stellate types, can be seen more easily at autopsy. This is a rather solid-looking lesion, red or cyanotic, without "spider legs" of the stellate type. They are 1-3 mm. in diameter and are not obliterated by pressure. They occur on the lips, tongue, face or fingers. Any site may bleed sometimes in the form of a sudden arterial spurting jet.

Pathology

The basic pathological change is a thinning of vessel walls with a deficiency of muscle leading to bulging[1]. Histologically the vascular wall is very thin, sometimes consisting of only a single endothelial layer lying immediately beneath a thinned out epidermis[36]. Bird and Jaques[27] emphasized that telangiectasia may primarily involve large and small veins, and arterial involvement can be inconspicuous. Bleeding results, according to Steiner[38], as capillaries of tiny veins are dilated with a single layer of endothelial cells without the addition of elastic or muscle fibers. They are thus weakened and subject to hemorrhage spontaneously or with slight trauma.

Diagnosis and Differential Diagnosis

The diagnosis of hereditary hemorrhagic telangiectasia is simple with the usual triad of habitual hemorrhage, multiple telangiectasia and family history. Errors all too commonly occur when small lesions are hurriedly overlooked[36]. The diagnosis is simple if kept in mind[35]. Do not hesitate to make the diagnosis in the absence of a family history as the previous cases may have been mild and the condition can skip a generation. It is amazing how often the diagnosis is overlooked.

Goldstein[33] has listed the diseases from which Rendu-Osler-Weber disease must be differentiated. These include hemophilia, pseudohemophilia, thrombocytopenic purpura, leukemia, anemia, tuberculosis, cirrhosis, malignancies, etc.

To us as gastroenterologists, the patient with melena or hematemesis presents his own peculiar intestinal challenge. Maloney[34] states that 80 per cent of upper gastrointestinal bleeding is from peptic ulceration, 5 per cent have intrinsic gastric lesions such as carcinoma or polyp and 5 per cent have portal hypertension with bleeding varices. Thus 10 per cent of all cases of gastrointestinal bleeding involves the rarer lesions where treatment depends on the exact location of the source of blood. Mucosal polyps, telangiectasias and tumors may produce lesions anywhere along the 24 feet of intestine and can escape careful examination by competent clinicians.

There are few surgical emergencies where there is more urgent need for a detailed history and meticulous physical examination. The therapy of shock is the only consideration taking precedence over this procedure[34].

When all gastrointestinal bleeders are considered, as our cases here, the rewards of a detailed history and examination are seen. A large group of the 10 per cent having a rare cause of gastrointestinal bleeding can be spared the inconvenience and negativity of extensive diagnostic tests. Examine your patients quickly but completely!

Treatment

Therapy is directed to control bleeding but is often incomplete. Rutin and ACTH[25] have been used as well as calcium, snake venom, sclerosing solutions, x-ray, radium and electrocautery. Topical thrombin[22], estrogen-androgens[31] and adrenochrome complex[25-32] occasionally are effective in stopping hemorrhages. Yet iron preparations and blood transfusions for anemia are the only universally accepted therapy. Multiple scattered telangiectasias emphasize the futility of any local removal of involved tissue except for possible control of the immediate bleeding site. Thus, on occasion, gastrectomy or colectomy may be life-saving as in our case. Resection of the stomach or an intestinal segment is justifiable only as a cause of uncontrollable bleeding. It is, however, difficult to be certain that the bleeding area is being totally excised—multiple telangiectasias through the whole gastrointestinal tract may be involved.

Less radical surgery such as ligation of vessels supplying an involved area of the stomach as adopted by Boston[10] must seldom be applicable. Cauterization of intragastric lesions as advocated by Shepherd[1] may help. The uncertain value of Rutin and other drugs believed to affect capillary fragility is apparent.

Prognosis

In the basic form, the disease is relatively innocuous, the telangiectasia causing little or no inconvenience[36]. The hemorrhages usually become more serious and recurrent with age[29] and are made worse by anemia, secondary to recurrent bleeding. The prognosis is sufficiently grave to demand our best therapeutic efforts[28]. The majority of patients at the time of their report are 42 years

of age and semi-invalids[28]. A discouraging feature in some cases is the appearance of new telangiectasias as quickly as old ones are destroyed[36].

Of 57 cases reported by Kelly[41], one died of epistaxis at age 48. Of 155 cases[28], five died of epistaxis at the average age of 48, one died of convulsions from cerebrovascular accident at age 3. Eight of 812 (4 per cent) died of the disease. A follow-up of other cases would probably show that many died prematurely, hemorrhages from all organs increasing in severity with middle life. A fatal hematemesis or melena rarely occurs although spontaneous cessation of bleeding is common!

Summary and Conclusions

The subject of gastrointestinal bleeding in hereditary hemorrhagic telangiectasia has been reviewed. Our first patient had 11 recurrent episodes of rectal bleeding over a ten-month period before right colectomy stopped her bleeding dramatically. Our second patient, asymptomatic with no family history of bleeding, demonstrated involvement of the small bowel and face.

This entity is usually overlooked in gastrointestinal hemorrhage, "hindsight being better than foresight" all too often.

There is a need for careful differential diagnosis in gastrointestinal bleeders with or without a family or hereditary history of hemorrhagic telangiectasia.

A review of published cases shows that gastroscopy, proctoscopy or laparotomy may be necessary to prove the diagnosis.

The purpose of our report is to alert the clinician to consider hereditary hemorrhagic telangiectasia in all cases of unexplained gastrointestinal bleeding and to examine the skin and mucous membranes most carefully.

Acknowledgment

Appreciation is gratefully extended to Dr. John F. Hardham of Paso Robles for referring Case 1 and to Miss Janet Ulmer who faithfully typed all manuscripts and helped in editing the case report.

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CLINICAL EVALUATION OF THE GASTROINTESTINAL TRACT IN THE AGED*

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Introduction

As the percentage of population over the age of 65 continues to rise, the study of geriatrics assumes greater significance. The Bureau of the Census reports that by 1975 there may be 20⅝ million people over the age of 65[1]. In studying the American literature, one is impressed by the relative paucity of adequate observations in large areas of clinical medicine relating to old people. There is a preponderance of articles dealing with cardiovascular and metabolic disease, which is in marked contrast to the gastrointestinal system.

TABLE I

Age Distribution of Patients

Age Groups	Male	Female	Total
65-69	3	0	3
70-74	10	7	17
75-79	22	21	43
80-84	19	8	27
85-89	5	4	9
90-94	2	1	3
	61	41	102

It is often stated that the gastrointestinal tract of the aged is different from the younger individual by virtue of "wear and tear" which allegedly characterizes the aging process. Holler[2] has observed mucosal atrophy, fatty degeneration, and thinning of the *muscularis propria* with aging, and Zeman[1] reports

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.

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atrophic changes of the mucus membranes and secretory cells. The increase in the incidence of achlorhydria with age is well known[3,4,5]. There also appears to be a decrease in digestive enzyme production, although a sufficient amount for ample digestion still remains[6]. In contrast to this, Palmer[7] after studying vacuum tube gastric mucosal biopsies concluded that the specimens taken from older individuals showed no more deviation from the usual or normal histologic picture than did specimens removed from younger people. Sklar[8] states that in the absence of disease, there is no impairment of motility, digestion and absorption, and Jordan[9] is of the belief that there is no reason for the gastrointestinal tract to be any different in the older individual.

Conflict of opinion obviously exists and it is our feeling that more adequate documentation in this field is warranted.

TABLE II

GASTROINTESTINAL SERIES

Age Groups	No. Cases	No. Abnormalities
65-69	3	3 —
70-74	16	10 (62.5%)
75-79	37	19 (51.4%)
80-84	26	18 (69.2%)
85-89	8	3 (37.5%)
90-94	2	1 —
	92	54

No. of Cases—92 Abnormal—54 (58.7%) 22 females
Normal—38 32 males

The present investigation is part of a program of clinical evaluation of aged individuals, the purpose of which is to determine those features which characterize the aged. In this study, we undertook to determine the clinical symptomatology of a group of old people who were essentially free of gastrointestinal disease, and to evaluate and compare their radiographic findings. The results have been compared to reported data on the general population.

METHODS AND MATERIALS

The subjects of this study consisted of 102 residents of a geriatric facility. The basis of selection was that the patient must have been: 1. sufficiently alert to furnish an adequate and reliable history, and 2. in relatively good health, with no recent evidence of significant gastrointestinal disease.

The ages ranged from 65 to 94 years; 82 patients being 75 years or older (Table I). Sixty-one patients were males and 41 were females. A complete history with detailed emphasis on the gastrointestinal tract was obtained. After a routine physical examination, an x-ray survey consisting of a gastrointestinal series, barium enema and gallbladder series was initiated. In some instances the radiographic studies were incomplete because the patient would or could not cooperate.

TABLE III

RADIOGRAPHIC FINDINGS—GASTROINTESTINAL SERIES

Diagnosis	Female	Male	Total
Esophageal diverticula	1	0	1
Gastritis	3	7	10
Hypertrophic	1	3	
Giant	0	1	
Antral	1	2	
Atrophic	1	1	
Prolapsed gastric mucosa	1	2	3
Cardiospasm	0	1	1
Deformed cap	4	5	9
Duodenal diverticula	3	2	5
Duodenal crater	0	2	2
Widened duodenal loop	0	3	3
Subtotal gastrectomy with gastroenterostomy	0	4	4
Small bowel deficiency pattern	0	1	1
Displacement of stomach by liver	2	0	2
Hiatus hernia	6	9	15

RESULTS

Gastrointestinal series:—Of the 92 gastrointestinal series performed, 54 (58.7 per cent) presented abnormalities (Table II). No correlation with age or sex is apparent. An analysis of these abnormalities is presented in Table III. The number of cases of prolapsed gastric mucosa is similar to the 2.5 per cent incidence quoted by Feldman[10] in approximately 12,000 gastrointestinal series performed on a representative group of the general population.

Our peptic ulcer findings consisted of 9 patients with deformed duodenal caps, 2 with actual craters, and 4 with a history of gastrectomy for the compli-

cations of peptic ulcer. This would bring the total peptic ulcer incidence to 14.7 per cent of our population. Cecil[11] states that 10 per cent of the population has evidence of peptic ulceration at autopsy. Muslow[12] reported that 10.5 per cent of ulcers occurred in patients over 60. Since radiographic studies accurately demonstrate only 80 to 85 per cent of lesions of the gastrointestinal tract[13], our figure would appear to show a somewhat greater incidence of peptic ulcer than that previously reported.

There was radiographic evidence of gastritis in 10 patients. While we agree with Sante[14] that hypertrophic and atrophic gastritis as diagnosed radiographically does not reflect the actual state of the gastric mucosa, these findings are offered not as a clinical diagnosis, but rather as a radiologic observation. According to Winklestein[15], chronic gastritis is extremely common in most people of middle or older age. Palmer's[5] findings, however, are at variance with this. He

TABLE IV

BARIUM ENEMAS

Diagnosis	Female	Male	Total
Diverticulosis*	10	13	23 (30.7%)
Sigmoid	5	11	16
Descending colon	2	1	3
Throughout	3	1	4
Irritable bowel	2	2	4
Total	12	15	27
No. of Cases—75	Abnormal—27 (36%) Normal—48		12 females 15 males

*7 of these cases (4 females, 3 males) showed irritability in addition.

feels that generalized alteration of the gastric mucosa is a consequence of disease rather than years.

The presence of duodenal diverticula in 5 patients is very similar to the 5 per cent incidence noted by Texter[16].

Of the 3 patients who had widened duodenal loops, one was proven to have carcinoma of the head of the pancreas which was asymptomatic. The others were followed both clinically and radiographically for nine months and no subsequent changes were noted.

A follow-up on both patients showing a displaced stomach failed to reveal any specific cause.

The most common nonmalignant x-ray change in the stomach of old people is hiatus hernia[17], which was present in 16.3 per cent of studies. This is higher

than the incidence of 2-9 per cent which has been previously reported in two large series[18,19]. The usual predominance of females[20] was reversed, 6 of our cases being males. All the hernias were through the esophageal hiatus, and, in the majority of instances, produced no symptoms, and would probably have remained undetected in the absence of x-rays.

The patient with cardiospasm had had esophageal dilatations in the past, and at the time of examination had minimal symptoms.

Barium enemas:—The results of the radiographic examinations of the colon are presented in Table IV which shows 36 per cent of enemas to be abnormal.

The presence of colonic diverticula in 30.7 per cent of patients is striking and is in marked contrast to the estimate of 5.6 per cent in all ages quoted by Rankin and Brown[21]. Monroe[22], however, is convinced that every patient over

TABLE V

DIVERTICULOSIS

Age Groups	No. Cases	Divertic. Present
65-69	3	0 —
70-74	9	3 (33.3%)
75-79	30	6 (20.0%)
80-84	24	10 (41.7%)
85-89	6	3 (50.0%)
90-94	3	1 —
	75	23 (30.7%)

the age of 61 years has diverticulosis, and Snell[23] descriptively states that after the age of 50, diverticula are as common as gray hair and wrinkles. In the literature[24] and also in our series, there appears to be an increased incidence with age (Table V). Diverticula are frequently seen at the point of exit of a blood vessel which may be regarded as a weakened portion of the intestinal wall. The degenerative changes noted in older people might enhance this weakness, and therefore might help explain the high incidence in the aged[18].

Seven of our patients had radiographic evidence of increased irritability of the colon in the region of the diverticula, a finding which is compatible with the diagnosis of diverticulitis. Since diverticulitis occurs in 10-25 per cent of individuals with diverticulosis[25,26], our figure does not differ from that of the general population.

The presence of an irritable bowel in 4 patients does not appear to be unusual.

Gallbladder series:—The results of 93 cholecystograms are presented in Table VI demonstrating abnormalities in 38.7 per cent of individuals examined. This is greater than the 12.7 per cent of diseased gallbladders noted in aged autopsied individuals by Monroe[27]. Practically all his cases were associated with calculi, whereas in our series only 14 per cent showed stones. This latter figure is lower than the 36-75 per cent[28,29,30] incidence of stones reported in the aged by other authors, and is equal to the 11.6 noted by Lieber[31] in a study of almost 30,000 autopsies in individuals over the age of 20 years.

Our actual incidence of stones is probably higher if three additional factors are taken into account. Firstly, that patients with active gallbladder disease were omitted from this series; secondly, that some of the patients with non-

TABLE VI

RADIOGRAPHIC FINDINGS—GALLBLADDER SERIES

	Female	Male	Total
Normal	17	40	57 (61.3%)
Abnormal	19 (52.8%)	17 (29.8%)	36 (38.7%)
Poor or non-visualization	10	12	22
Poor or non-visualization + stones	3	1	4
Stones	5	4	9
Diverticulum	1	0	1
Total	36	57	93 (100%)

14.0% of patients had stones
(22.2% females; 8.8% males)

visualizing gallbladders had nonopaque calculi, and thirdly, that some of the seven patients who had undergone cholecystectomy for gallbladder trouble in the past, and who were not included in the statistics, had biliary calculi present at the time of surgery.

The commonly accepted age and sex correlation of gallbladder disease is confirmed in this study[31,32]. As the age increases, so does the incidence of abnormal cholecystograms (Table VII). The incidence of abnormal cholecystograms was 52.8 per cent in females and 29.8 per cent in males. The difference was even greater in the case of gallstones; females 22.2 per cent, males 8.8 per cent.

A comparison with another study in the aged[33] and a large series of gallbladder x-rays[34] would be invalid because the individuals examined were chosen for the most part because of complaints.

Composite radiographic findings:—Of the 260 radiographic procedures performed, 45 per cent revealed some abnormalities, the gastrointestinal series showing the highest incidence of positive findings (Table VIII).

The gallbladder, gastrointestinal and barium enema studies were completed in 64 patients; 78.1 per cent had findings on x-ray; 9 per cent of the 64 patients showed abnormalities in all three studies. In this group of individuals there were no instances of Saint's Triad (colonic diverticula, gallstones and hiatus hernia). This is interesting in light of a recent report by Foster and Knutson[35] in which they found a higher incidence of this triad in the older population.

TABLE VII

RADIOGRAPHIC FINDINGS—GALLBLADDER SERIES
AGE DISTRIBUTION OF ABNORMALITIES

Age Groups	No. Cases	No. Abnormalities
65-69	3	1 —
70-74	15	4 (26.7%)
75-79	40	13 (32.5%)
80-84	25	12 (48.0%)
85-89	7	4 (57.1%)
90-94	3	2 —

SYMPTOMATOLOGY

Early in the study it became evident that clear-cut complaints were generally associated with pathologic states demonstrated radiographically. On the other hand, the absence of symptoms was not necessarily indicative of radiographic findings. It is our impression that the frequency of vague and equivocal gastrointestinal complaints was no greater in this series than in younger age groups. Snell[23] in a study of over 300 patients over 65 years of age who were seen in a gastrointestinal clinic, concluded that the aged have many complaints without adequate pathologic basis. Sklar[8] too found that the majority of patients had no organic disease to which their symptoms could be attributed.

Our experience is similar to that of Zeman's[35] who states that "contrary to the usual belief, old people do not complain enough; with age there is a tendency to accept pain and discomfort as inevitable". It should be mentioned that the great majority of our patients migrated from eastern Europe to escape

oppression in their native lands. Perhaps the hardships suffered inured them to discomfort, or rendered them less likely of adequately verbalizing their complaints.

The most common complaint was that of constipation which was present in 43.1 per cent of patients (Table IX). This figure is somewhat higher than the incidence of 25-35 per cent[6,37] reported in older people. Although constipation is regarded as a disease primarily of old people, Walsh et al disagree[38] after a study in which they found that 31 per cent of college students complained of constipation. In contrast to the general belief that constipation occurs much more frequently in females, our series revealed a relatively equal sex distribution. Factors which contribute to the large number of individuals who are constipated are decreased intestinal secretions, decreased peristalsis, loss of

TABLE VIII

SUMMARY OF RADIOGRAPHIC FINDINGS

Type of Examination	Normal	Abnormal	Total Number
Gastrointestinal series	38 (41.3%)	54 (58.7%)	92
Gallbladder series	57 (61.3%)	36 (38.7%)	93
Barium enema	48 (64.0%)	27 (36.0%)	75
Total	143 (55%)	117 (45%)	260 (100%)

abdominal wall tone, and decreased nervous sensibility[3]. Meuller-Deham[37] feels that the lack of bulky foods in the diet which stimulate peristalsis may also be of some significance.

Altered taste perception was the complaint of 34.3 per cent of patients (Table X). The various complaints are listed, bitter being the most frequent complaint elicited. A detailed analysis of taste perception in the aged is a subject of another report[39]. The findings may be briefly summarized as follows: 1. There is no significant decrement in gross taste perception with aging. 2. There is no relationship between oral complaints and taste perception. 3. Complaints referable to taste were far more common in the aged than in the younger group.

The only other complaint of significance was poor appetite which was present in 15.7 per cent of patients (6 females, 10 males). Some of the patients,

however, admitted that their appetite loss was due to a dislike for institutional food rather than an actual loss of desire to eat. Although some authors[40,41] feel that appetite is generally well preserved in old people, others state that the aged have a poor appetite attributable to a decreased sense of smell and taste[42] and diminished diencephalic activity[43].

The various other complaints as recorded in the 64 patients who completed the radiographic studies are listed in Table XI. In almost all instances the complaints were vague and not severe enough to warrant the patient's requesting medical care from the house staff.

Thirteen of the 14 patients who had completely normal x-rays were in the asymptomatic group of patients. Yet despite the fact that there were twice as

TABLE IX

CONSTIPATION

Age Groups	No.	Per cent
65-69	0	—
70-74	5	29.4
75-79	19	44.2
80-84	14	51.9
85-89	4	44.4
90-94	2	—

44 (43.1%) patients were constipated
18 females (43.9%), 26 males (42.6%)

many patients in the asymptomatic as compared to the symptomatic group, the number of patients who showed abnormalities in all radiographic studies was equal, 3 patients in each category.

PHYSICAL FINDINGS

There were two significant physical findings related to the gastrointestinal tract noted in subjects in this series (Table XII).

Hemorrhoids were present in 52.9 per cent of individuals with a similar sex distribution. Although Bacon[44] states that this condition is seen more commonly in males, Lewis'[45] conclusions are in agreement with ours. The latter author, however, found an increasing frequency with age in contrast to our lack of age correlation in this study. Constipation which is considered to be a significant etiologic factor[45], was present in 68.8 per cent of patients with hemorrhoids. Inadequate muscle support, sphincteric atrophy[46], and loss of tone[47] are possible contributory factors.

Hernias in the abdominal wall were present in 17.6 per cent of patients, an incidence which is very similar to Monroe's[48]. It is our impression that this incidence is greater than that seen in the general adult population. The male

TABLE X

ALTERED TASTE

Age Groups	No.	Per cent	Taste Complaints	
65-69	2	—	Bitter	18 (17.6%)
70-74	9	52.9	"Peculiar"	6
75-79	9	20.9	Dry	6
80-84	11	40.7	Sour	3
85-89	2	22.2	Burning	1
90-94	2	—	Salty	1
			Total	35

Altered taste in mouth—35 (34.3%)

16 females
19 males

sex was responsible for 83.3 per cent of them. Thirteen (72.2 per cent) of the hernias were of the inguinal variety, two were ventral, two were umbilical, and one was femoral. This is in conformity with frequency of inguinal hernia (80 per

TABLE XI

64 PATIENTS WITH COMPLETED RADIOGRAPHIC STUDIES

Symptoms	(Present in 27.9%)
Cramps	12
Heartburn	10
Belching	3
Vomiting	2
Nausea	1
Bloating	1
Diarrhea	0
Tarry stools	0

Radiographic findings—present in 78.1%.

cent of all hernias) previously reported[49]. Here, too, the aging process with devitalization of muscle, aponeurotic tissue, and fascial structures seem to be implicated as causative factors[50].

Summary and Conclusions

1. The general impression that the older individual has numerous complaints referable to the gastrointestinal tract (with the exception of constipation and altered taste) is not confirmed.

2. In the 102 patients examined, there were radiographic findings in 45 per cent of patients. Of the 64 cases who completed 3 radiographic studies, 29.7 per cent had complaints (except for constipation and altered taste) referable to the gastrointestinal tract, usually of a mild nature. Yet 78.1 per cent of these 64 patients had positive radiographic findings.

3. In general there is some, but not a striking increase in abnormalities as the patient grows older. Gallbladder disease, hiatus hernia, colonic diverticula, inguinal hernia, and external hemorrhoids are the prevalent findings in this group. The latter four conditions imply a relationship to degenerative changes associated with aging.

TABLE XII

Significant Gastrointestinal Clinical Findings

Age Groups	No.	Per cent
65-69	0	—
70-74	10	58.8
75-79	21	48.8
80-84	16	59.3
85-89	6	66.7
90-94	1	—
Hemorrhoids—54 patients (52.9%)		25 females 29 males
Hernia—18 patients (17.6%)		3 females 15 males

4. The incidence of gallstones noted in this series is lower than that generally reported for this age group.

5. Occult carcinoma was found in only 1 out of 260 radiographic procedures.

Acknowledgment

The authors wish to express their gratitude to Mr. Howard M. Kalb, B.B.A., M.S., for his aid in the preparation of the data.

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THE CORTICOSTEROID-INDUCED PEPTIC ULCER: A SERIAL ROENTGENOLOGICAL SURVEY OF PATIENTS RECEIVING HIGH DOSAGES*

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During a period of two and one-half years, 77 patients, who were candidates for or were receiving steroid therapy, were observed for peptic ulcer. Most of them were examined roentgenologically at 3-month intervals. This made it possible to correlate ulcer incidence with dose, duration of therapy and effect of individual drugs, as well as to add to the very sparse information upon

Fig. 1

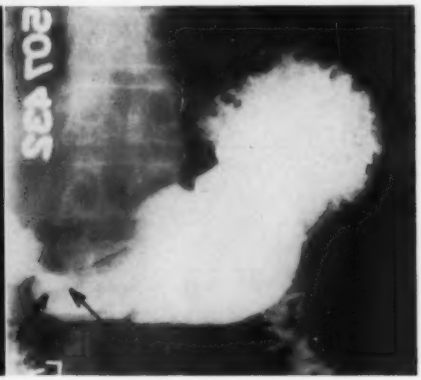

Fig. 2

Fig. 1—Base line normal study (T.F.).
Fig. 2—After 3 months of steroid therapy, development of a moderate size, shallow, prepyloric ulcer (T.F.).

behavior of ulcers during continuous steroid administration. Almost all of the patients had systemic *lupus erythematosus* and required large amounts of steroids. The incidence of peptic ulcer in this treated group was compared with the incidence in a similar group of patients not receiving these hormones. Since

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September, 1959.
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This study was supported by grants from Lederle Laboratories and the Upjohn Company.

there are relatively few reports of roentgenological surveys of patients treated with steroids, and none with such extensive serial studies on patients receiving high dosage, it was thought that presentation of our findings and comparison with previous data would be of interest.

TABLE I

SUMMARY OF LITERATURE SHOWING RELATIVELY LOW INCIDENCE OF PEPTIC ULCER DURING STEROID THERAPY

Authors and date of report	No. of patients	% incidence of ulcer	Remarks
Arbesman, Richard[3] 1954	75	0	Asthmatics on cortisone. Dosage sometimes intermittent. Average maintenance dose from 50-75 mg. per day.
Henderson[4] 1955	1,440	5.3	No dosage correlation. Figures based on survey of literature.
American Rheumatism Assn.[5] 1955	564	6.6	Figures from questionnaires. On doses of 50 mg. or less of cortisone per day incidence of ulcer was 4.4 per cent, while on doses of more than this it was 8.3 per cent.
Bunim, Ziffe, McEwen[6] 1955	64	7.8	While the over all incidence of ulcer was low, the only 3 patients to receive more than 100 mg. cortisone daily all developed ulcer and 2 perforated.
Boland[7] 1956	141	4.9	Gastric complaints in 26 patients. Gastrointestinal series on these showed 7 ulcers. Dose 8-14 mg. prednisone or prednisolone. Adverse reactions of all kinds increased with dose increase.
Kirsner, Sklar, Palmer[8] 1957	180	0	Cases of chronic ulcerative colitis. Initial large, but smaller maintenance doses cortisone. Long treatment time.
Meltzer et al[9] 1958	115	Under 3.6	All examined roentgenologically. Average dose 13.8-14.2 mg. prednisone.

Up to 1954, Sandweiss[1] and Wollaeger[2] were able to collect from the literature only 50 to 55 instances of peptic ulcer occurring during steroid therapy. Since then the reported incidence has varied from 0 to 31 per cent. The more widely quoted reports and all roentgenological surveys have been tabulated in Tables I and II. Table I comprises those reporting a relatively low and Table II

those reporting a relatively high incidence of ulcer. It was thought that such a division might emphasize variations in dosage, length of treatment or effect of individual drugs if such exist.

In Table I, ulcer incidence varies from 0 to 7.8 per cent. It is noted that in most reports patients were receiving cortisone and that, using generally accepted dosage equivalents, the amounts of drug were far less than is the case in Table II. There seems to be some dose:ulcer incidence correlation in the report of the American Rheumatism Commission[5] which shows that the incidence of ulcer in patients receiving more than 50 mg. of cortisone was nearly double that in those receiving less than this amount. Bunim et al[6] comment that the only three patients in their group of 64 to receive more than 100 mg. of cortisone all developed an ulcer. No conclusions can be drawn regarding length of therapy and its relation to ulcer incidence from Table I.

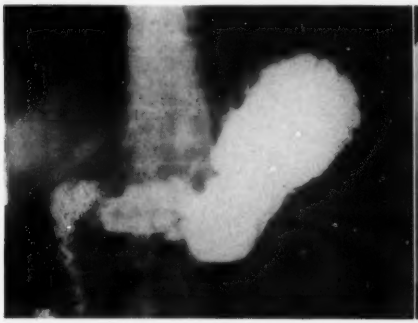

Fig. 3

Fig. 4

Fig. 3—Within 4½ months, healing, but residual mucosal changes compared to normal base line study (T.F.).

Fig. 4—Large, lesser curvature, antral ulcer (E.M.).

In Table II, the reported ulcer incidence varies between 12.5 and 31.0 per cent. Kern, Clark and Lukens[12] and Kammerer et al[17,18] both show a rather clear cut increase in ulcer incidence with increasing steroid dosage. The data of the latter workers is especially striking both as to total ulcer incidence and dosage correlation. They report an over all incidence of 31 per cent. When a dosage of 10 mg. of prednisone or its equivalent was given there was an almost tenfold increase in ulcer incidence over those given lesser amounts. All of their patients had received steroids for six months or more, and a single roentgenologic study was made of each patient. Prolongation of therapy beyond six months did not affect ulcer incidence. Gedda and Moritz[16] found an increased risk of peptic ulcer with increasing length of treatment. Others failed to make such a correlation.

TABLE II

SUMMARY OF LITERATURE SHOWING RELATIVELY HIGH INCIDENCE OF PEPTIC ULCER DURING STEROID THERAPY

Authors and date of report	No. of patients	% incidence of ulcer	Remarks
Bollet, Black and Bunim[10] 1955	18	16	Serial gastrointestinal studies on all patients. Two of the 3 ulcer patients had negative pretreatment studies. All ulcers asymptomatic and occurred on doses of 25-30 mg. daily prednisone or prednisolone.
Howell and Ragan[11] 1956	75	26	No precise dose: incidence relationship. Doses generally 43-75 mg. cortisone or 10-25 mg. prednisone or its equivalent daily. Often only slight epigastric distress with objective ulcer. Ulcers occurred 5-30 months after initiation of therapy.
Kern, Clark and Lukens[12] 1957	169	12.5	Three of 14 patients developed ulcer on 20 mg. or more prednisone daily. No ulcer in 54 patients with dose of 15 mg. or less. No definite relationship between length of therapy and development of ulcer. Statistical analysis indicates a 20-60-fold increase over normal expectation of ulcer development.
Black, Yielding and Bunim[13] 1957	39	16	Doses of prednisone over 20 mg. per day.
Hilbish and Black[14] 1958	49	24	This data is from review of all steroid-treated patients at National Institutes of Health. Atypical ulcer symptoms. Time-dose relationship to ulcer variable, but most patients received over 15 mg. prednisone daily. Two fatal hemorrhages from steroid-associated ulcers.
Evans[15] 1958	23	26	All patients studied roentgenologically. One-third asymptomatic. Average dose 20 mg. prednisone daily.
Gedda and Moritz[16] 1958	69	19	All patients studied roentgenologically. Doses of 5-15 mg. prednisone daily for at least 6 months. Length of treatment increased ulcer risk. Often slight symptoms. Control group of autopsied rheumatoid arthritis, 31 in number—10 per cent ulcer.
Kammerer, Freiberger, Rivelis[17,18] 1958	117	31	All patients treated 6 months or more. Forty per cent asymptomatic. Dose and relation to ulcer incidence (prednisone equivalent, mg./day): 2.5-7.5 mg. — 4.7 per cent ulcer (21 patients) 10-15 mg. — 45.0 per cent ulcer (61 patients) Over 15 mg. — 40.0 per cent ulcer (6 patients) Control group of 33 patients—9 per cent ulcer. Single roentgenologic study of each patient.

Since we employed roentgenological methods of diagnosis, we were particularly interested in studies using similar diagnostic criteria. Bollet, Black and Bunim[10], Evans[15], Gedda and Moritz[16] and Kammerer et al[17,18] reported ulcer incidences of from 16 to 31 per cent. In each of the studies, the authors remarked upon the frequency with which the patients were asymptomatic or had symptoms atypical for ulcer in the face of an objectively demonstrated lesion. The only radiologic survey showing an extremely low incidence of ulcer is that of Meltzer et al[9]. In this study there was no obvious variation in dose, duration of treatment or individual drug to explain this.

Materials and Methods

Seventy-seven patients from the Collagen Disease Clinic of the Los Angeles County General Hospital were studied. Sixty-three of them received steroid

Fig. 5

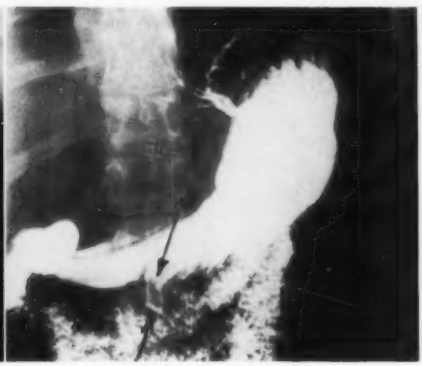

Fig. 6

Fig. 5—Base line normal gastrointestinal study after 16½ months of steroid therapy (Z.K.).
Fig. 6—Within 6 weeks of increased dosage of steroid therapy, development of a penetrating greater curvature ulcer (Z.K.).

therapy. All but two were ambulatory outpatients. Eight—one per cent were female. Aside from three cases of rheumatoid arthritis and four of other collagen diseases, they were diagnosed as having systemic *lupus erythematosus*. An attempt was made to examine all patients roentgenologically prior to instituting steroid therapy, but, since many were on such treatment when the study began and others required therapy immediately, this was achieved in only 41. Once steroid therapy had begun, serial roentgen studies were performed at intervals of approximately three months. The program was carried on for two and one-half years and the 77 patients received a total of 243 examinations (Table III). Only two of the 14 patients who did not receive steroids were examined more than once. Although a patient receiving over 10 mg. per day of prednisone or

its equivalent in our Clinic normally is placed on a prophylactic ulcer regimen, such prophylaxis was given in only seven of the 77 patients in this series. One of the seven had a pre-existing peptic ulcer. Four were on unusually high dosage of steroids. Another had gastrointestinal symptoms prior to our study and the final patient had been on a prophylactic ulcer regimen elsewhere.

Results

1. Base line studies or control group:—In the 41 patients examined prior to institution of steroid therapy, only two (approximately 5 per cent) showed any roentgenological abnormality. In each case this consisted of deformity of the duodenal bulb. One of these patients showed no change during steroid therapy

TABLE III

Frequency of Serial Gastrointestinal Studies

Number per patient	Numbers of patients
1	20
2	20
3	9
4	10
5	4
6	8
7	4
8	3
9 or more	2

Total number of gastrointestinal studies—243.

while the other developed active ulceration. Fourteen of this group of 41 patients did not receive steroids while the others were so treated subsequent to their base line examination.

2. Steroid treated patients examined roentgenologically:—Of the 63 patients receiving steroid therapy, 48 showed no evidence of active peptic ulceration. The comparative therapeutic data in this group and in those with positive evidence of ulcer is presented in Table IV. Drug dosage was higher and duration of therapy longer in the group developing ulcer.

Active peptic ulcer was demonstrated roentgenographically in 15 patients. In addition, two patients with normal radiographic findings were diagnosed as

having peptic ulcer for a total incidence of 27 per cent. One was so diagnosed on the basis of a perforated duodenal ulcer proven at autopsy, the other on the basis of repeated episodes of massive hematemesis. The data on all patients developing ulcer is presented in Table V.

a. Location and radiologic appearance of ulcers:—Ten ulcers were gastric and six duodenal. Eight of the gastric ulcers were in the distal stomach, and only two in its mid portion (see Figs. 1-4). One was located on the greater curvature (see Figs. 5-9). In one-half of the cases, the ulcers were shallow and surrounded by mucosal edema as emphasized by other workers[17,18]. In the others, however, the appearance was not different from the usual gastric ulcer. In a few cases where many examinations were performed, mucosal changes, presumably based upon edema, preceded appearance of the niche. This was also demonstrated in one case of duodenal ulcer (see Figs. 10-12). The other four

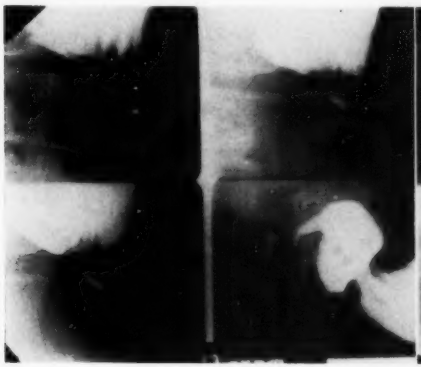

Fig. 7

Fig. 8

Fig. 7—Spot films of Fig. 6.
Fig. 8—Two months after appearance of greater curvature ulcer, reduction in its size (Z.K.).

duodenal ulcers were not unusual in appearance or location. Only one diagnosis of ulcer was made without demonstration of a niche. In this case a normal gastrointestinal study was followed by observation of a deformed duodenal bulb.

b. Sex incidence of peptic ulcer in steroid treated patients:—Of 12 males, five (41 per cent) developed ulcer, while in 51 female, 12 (24 per cent) were shown to have peptic ulcer.

c. Correlation of ulcer incidence with length of treatment:—The duration of steroid therapy in patients showing peptic ulcer is given in Table V and the duration of such therapy in patients developing ulcer as compared with those who did not in Table IV. In all but six instances, steroid therapy had been administered for more than six months before peptic ulcer was diagnosed. The

TABLE IV

COMPARATIVE THERAPY IN ULCER AND NONULCER PATIENTS

RESULTS OF ROENTGENOLOGIC STUDIES CORRELATED WITH DRUG, DOSAGE, AND DURATION OF OBSERVATION

	Patients with ulcer								Patients with no ulcer shown			
Steroid	No. of patients receiving drug	Median duration steroid therapy, months to last x-ray	Total patient months x-ray observation	Patients	%	Dose range 4-8 weeks prior to demonstration active ulcer mg./day	Median dose mg./day	Average period x-ray observation, months	No. of patients	Dose range during x-ray observation	Median dose mg./day	Average period x-ray observation, months
Prednisone and prednisolone	27	10	98	5	18.5	12.5-100	40	4.8	22	10-50	30	3.2
Methylprednisolone	18	12.5	94	4	22.0	36-144	60	3.7	14	8-48	20	5.6
Triamcinolone	23	21.5	169	4	17.4	12-96	40	13.7	18	8-100	28	6.3
Dexamethasone	17	8	45	2	*	3.5-18	10.7	6.5	13	0.5-8.0	3	2.2
Total	85**		408	15					67			

*Period of study much too short to draw conclusions. See addendum.

**A number of patients received more than one steroid.

minimum time for the roentgenographic appearance of an ulcer was two months. It is noteworthy that in this exceptional case a dose of 144 mg. methylprednisolone was administered daily. From Table IV, it is evident that the average period of steroid treatment under roentgenologic observation was considerably longer in the patients developing ulcer than in those with normal roentgen studies.

d. Correlation of ulcer incidence with dose:—The specific dosage data for each patient developing ulcer is given in Table V. The considerably higher median dose and the dose ranges in the patients with ulcer compared to those not developing ulcer is demonstrated in Table IV. Table VI, however, presents the most striking correlation of steroid dosage with ulcer incidence. Since there was no difference in occurrence of peptic ulcer on various drugs, dosage

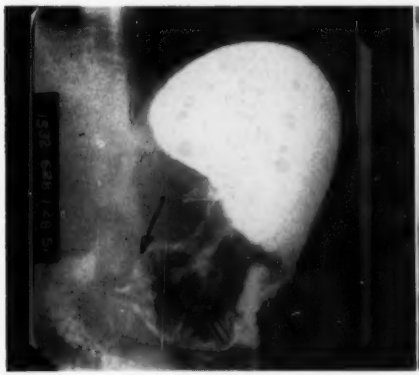

Fig. 9

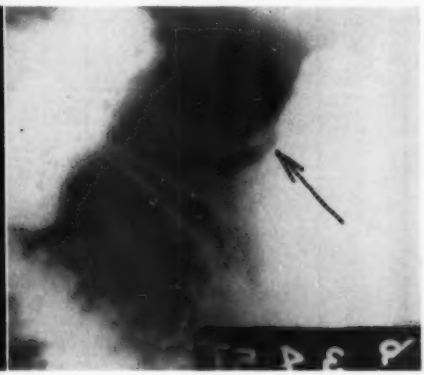

Fig. 10

Fig. 9—Only radiating folds to indicate site of greater curvature ulcer. Note development of entirely new, small, lesser curvature antral ulcer. Coincident with appearance of second ulcer, observe change in contour of distal stomach compared with previous studies (Z.K.).

Fig. 10—Spot films of second ulcer—small, antral, on lesser curvature (Z.K.).

is expressed in milligrams of prednisone equivalent by use of conversion factors appended to Table VI. Ulcer incidence of 23 per cent with dosages of 40-49 mg./day and of 47 per cent with dosages over 60 mg./day furnishes a striking correlation. The minimum dose of individual drugs (mg./day) associated with occurrence of peptic ulceration is: prednisone and prednisolone 12.5; triamcinolone 32.0; methylprednisolone 36.0; dexamethasone 3.5. Although the dose for prednisone seems lower than the rest, this difference is only suggestive. Two patients who were receiving 12.5 and 15 mg. of this hormone per day immediately, prior to their initial base line x-rays had ulcers demonstrated. Both had received larger doses of this hormone many months before their examination.

TABLE V

PEPTIC ULCERS OCCURRING DURING STEROID THERAPY

Patient	Normal base line study	Steroid administered and dose (mg./day) during the 4-8 week period prior to demonstration of the ulcer.	Duration steroid therapy before ulcer, mo.	Description and location of niche	Healing and/or behavior of ulcer	Remarks	Prophylactic regimen	Symptoms	Therapeutic regimen
Z.K.	Yes	Prednisone 60	18	Initial ulcer on greater curvature fundus. Second ulcer—antral on lesser curvature.	Initial ulcer showed variable behavior, finally healing in 7 mos. Second ulcer healed in 11 mos.	Reduction in steroid dosage after appearance of each ulcer. Change of drug to cortisone 80 mg. after initial lesion hence second ulcer developed while on this therapy.	0	+	+
T.F.	Yes	MK 117 20	3	Moderate size, prepyloric.	Healing in 5½ months.	16 alpha hydroxy hydrocortisone 20 mg./day during healing.	0	+	+
S.R.	Yes	Prednisone 20	18	Duodenal.	Fully healed in 4 months.	8 gastrointestinal studies before appearance of crater. Mucosal change preceded niche.	0	+	+
J.G.	Yes	Methylprednisolone 64	6	Duodenal.	Healing in 5 weeks.	Reduced dose and change of steroid after ulcer. Melena at time of diagnosis.	+	+	+
O.J.	Yes	Triamcinolone 48	10	Small, prepyloric.	Healing in 5 months.	Mucosal changes preceded niche. Dose of steroid unchanged during healing.	0	0	0
M.P.	Yes	Methylprednisolone 36	7	Moderate size, antral lesser curvature.	Fully healed in 3 months.	Psychosis—No symptoms.	0	?	+

R.M.	Yes	Methylprednisolone 144	2	Lesser curvature, mid fundus.	Healing in 2 months.	Psychosis—No symptoms. Reduced dose of steroid during healing.	+	?	+
D.M.	Yes	Dexamethasone 3.5	16	No crater. Normal bulb, then deformity 6 mos. later.	Repeated examinations merely confirmed deformity.	The only roentgenologic diagnosis made without demonstrating crater.	0	+	+
L.J.	No	Methylprednisolone 56	2½	Small, prepyloric lesser curvature.	Healing in 5 months.	Healing on 10 mg. dexamethasone.	0	0	0
A.C.	No	Prednisone 12.5	9	Small, prepyloric, lesser curvature.	No healing over a 10-month period.	Steroid changed to 8 mg. methylprednisolone.	0	+	
E.M.	No	Cortisone 100	6	Lesser curvature, antral.	Healing in 7 months.	Reduced steroid dose during healing.	0	+	+
P.B.	No	Cortisone 75	72	Duodenal.	Not observed.		0	+	+
E.B.	No	Prednisone 15	36	Duodenal.	Healed in 2 months.	Parenteral cortisone during healing.	0	+	+
B.B.	No	Triamcinolone 32	9	Small, pyloric.	Healing within 1 year.	Reduced steroid dose during healing.	0	0	0
J.W.	No	Triamcinolone 12	4	Initial ulcer pyloric. Second pyloric ulcer 4 mos. after healing of 1st.	Initial ulcer healed 2½ months.	Known previous ulcer and deformed bulb at start of steroid therapy. Reduced steroid dose during healing.	+	+	+
R.B.		Triamcinolone 32	4	Normal roentgenologic study. 2 mos. later death.	Autopsy proven perforated duodenal ulcer.	Prednisone 100 mg./day given latter part of 4 mos. period of observation.	+	+	+
S.S.		Dexamethasone 18	4	Two normal roentgenologic studies.	2 episodes of massive hematemesis.	Ulcer regimen. Hematemesis subsided as did symptoms.	0	+	+

e. Behavior of ulcers:—In the single patient who showed a deformed bulb following a normal gastrointestinal study, repeated examinations showed only persistence of the deformity. One patient was lost to observation following demonstration of a single active ulcer. Another showed a persistent niche for ten months. Twelve patients who were followed by serial roentgenological studies after the appearance of an active ulcer showed healing, and this observation of behavior is one of the unique features of this study. The healing time and management during healing in these patients is given in Table VII. Among the 12 patients, perhaps the most unusual phenomenon is that in two instances (O.J. and L.J.) healing occurred at the end of five months without either an ulcer regimen or reduction in steroid dosage, and both were asymptomatic. The

Fig. 11—Base line normal. Note mucosa of duodenal cap (S.R.).

ulcers in the other 10 patients healed with reduced steroid dosage and/or administration of an ulcer regimen. Healing time was variable and in the majority was between five and 12 months. While healing was observed, it must be remembered that there were two patients with recurrence of ulcer and that ulcer behavior was most unfavorable in two additional patients with one instance of repeated hematemesis and one fatal perforation.

f. Association of ulcers with symptoms:—Two patients with peptic ulceration were asymptomatic. Two others were psychotic. In the rest of the group (76 per cent) subjective manifestations varied from classic postprandial pain relieved by food to heartburn and vague upper abdominal distress. When gastrointestinal complaints in the nonulcer as well as the ulcer groups were tabulated,

it was found that, of a total of 63 patients treated with steroids, 28 had gastrointestinal symptoms. Twelve of these had peptic ulcer and 16 did not. There was no variation in incidence of subjective distress when one steroid was compared with any other. Generally, the occurrence of symptoms coincided with positive roentgen findings but, in one case, symptoms preceded demonstration of an ulcer by seven months.

g. Influence of a prophylactic ulcer regimen:—Four of the patients developing peptic ulcer had received a prophylactic ulcer regimen for some time

TABLE VI

CORRELATION OF STEROID DOSAGE AND ULCER INCIDENCE

Dosage in mg./day expressed as prednisone equivalent	Total number of patients	Number of patients developing ulcer	Percentage of patients developing ulcer
Under 10	6	0	0
10-19	23	3	13
20-39	26	1	4
40-59	13	3	23
Over 60	17	8	47

CONVERSION DATA FOR INDIVIDUAL STEROIDS

Steroid	Equivalent Units
Prednisone and Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75
Cortisone	25
Hydrocortisone	20

prior to the demonstration of the lesion. One of these had a known gastric ulcer two years before steroid therapy and a deformed bulb when therapy was initiated. The others were the patients receiving the highest dosages of steroids in the entire group—prednisone 100 mg., triamcinolone 96 mg. and methylprednisolone 144 mg. per day respectively. Only three patients in the nonulcer group received prophylaxis.

Comment

Early reports of a low incidence of steroid-associated peptic ulcer (up to 7.8 per cent), largely on low dosages of cortisone, have not been confirmed by more recent investigations where higher doses of newer steroids have been employed (up to 31 per cent). Using prednisone equivalent in mg./day, Kern et al[12] found an ulcer incidence of approximtely 20 per cent when 20 mg. or more was administered and 0 per cent with 15 mg. or less, while Kammerer et al[17,18] cited an almost tenfold increase in incidence when doses of more than 10 mg. were compared with amounts less than this. Roentgenologic surveys especially have, with one exception, shown incidence of from 16 to 31 per cent. Correlation of ulcer occurrence with length of treatment is not so clear, although in the series with the highest rate of ulceration, all patients were treated for more than six months.

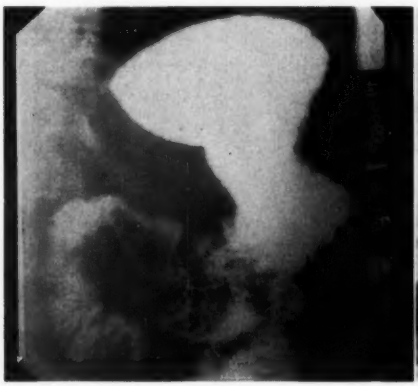

Fig. 12

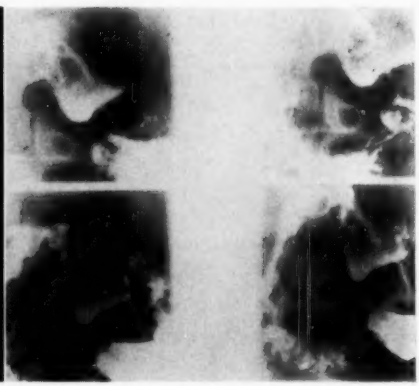

Fig. 13

Fig. 12—After 11 months of steroid therapy mucosal edema and equivocal shallow ulcer crater. Numerous preceding studies, not reproduced, showed gradual development of mucosal changes (S.R.).

Fig. 13—Crater on greater curvature aspect of bulb in its distal portion with marked mucosal edema (compare with base line) (S.R.).

In our series of 77 patients undergoing numerous roentgenologic examinations over a long period of time, there was no unusual incidence of ulcer in a control group, and an incidence of approximately 27 per cent during steroid therapy. One-half of the gastric ulcers varied in appearance from the ordinary type in that ulcerations were shallow and mucosal changes unusual. In a few cases with multiple examinations, mucosal changes were almost evolutionary, preceding and almost predicting appearance of a niche. Variability from the usual in location was evidenced by occurrence of one greater curvature ulcer and appearance of 80 per cent in the distal stomach. The frequency of gastric compared to duodenal ulcers was notable—2:1 as compared to the normal expec-

tation of 1:10. Most ulcers appeared after six months of treatment. Dose:incidence correlation was very significant, rising to 47 per cent with 60 mg./day or more of prednisone or its equivalent. Behavior of ulcers with continued steroid administration was interesting in that healing was usual, although five months or more were required in more than 60 per cent of instances. Laitinen et al[19] in seven patients observed fairly prompt healing under the same conditions. No other large series of observations upon ulcer behavior with continued steroid

TABLE VII

OBSERVATIONS ON HEALING OF ULCERS ASSOCIATED WITH STEROID THERAPY

Case No.	Time required for healing	Management during healing period
O.J. 30	5 mos.	Dose of steroid unchanged. No ulcer regimen.
L.J. 69	5 mos.	Change of drug, but equivalent dosage. No ulcer regimen.
B.B. 8	12 mos.	Reduced dose of steroid. No ulcer regimen.
J.G. 20	5 wks.	Change of drug with reduced dosage and ulcer regimen.
R.M. 36	2 mos.	Reduced dose of steroid. This patient was on prophylactic ulcer regimen because of the enormous dose of steroid administered.
E.B. 64	2 mos.	Change of drug (parenteral cortisone).
T.F. 18	5½ mos.	Change of steroid and ulcer regimen.
E.M. 46	7 mos.	Reduced steroid dosage and ulcer regimen.
Z.K. 33	7-11 mos.	Recurrent ulcer. Reduced steroid dosage and ulcer regimen.
J.W. 63	2½-6 mos.	Recurrent ulcers with healing under reduced steroid therapy. This patient had an ulcer history before steroid therapy and a deformed bulb at the start of treatment. She was on continuous prophylactic ulcer regimen.
M.P.	3 mos.	Reduced dose of steroid and ulcer regimen.
S.R.	4 mos.	Dose of steroid unchanged. Given ulcer regimen.

administration are known to us. Healing with continued therapy did not imply benignity or preclude recurrence. There were two recurrent ulcers and one fatal perforation. One instance of severe melena occurred at the time of demonstration of a crater, and in another patient severe hematemesis appeared in the face of negative roentgen studies. Sex incidence, higher in the male, correspond to the usual experience with peptic ulcer. Although the frequency of an asymptomatic state commented upon by other roentgenologists surveying steroid-treated patients was not confirmed, there were two patients with objective ulcer and

no symptoms in this series. Seventy-six per cent of our patients were asymptomatic. Only half of those with symptoms had ulcer objectively. While this study does not allow conclusions regarding the effectiveness of the usual ulcer regimen, either prophylactically or therapeutically, such regimen is to be recommended for both purposes, especially when higher doses of steroids are employed (over 10 mg./day of prednisone or its equivalent).

The significance of the steroid-induced ulcer problem can best be realized if one attempts to compare the increase in incidence of peptic ulceration during the short period of steroid therapy, with the normally expected occurrence of ulceration in these patients or in a closely allied disease, rheumatoid arthritis. In a careful study in England, it was determined that the expectation rate of developing a new peptic ulcer in men between the ages of 35 and 64 was 0.327 per cent per year[20]. Since the incidence in males in our series during their treatment period of approximately one year was 41 per cent, or about 33 per cent more than the average expected incidence of 7.5 per cent for males with non-steroid-treated rheumatoid arthritis, the rise in risk during their year of steroid treatment is about 100-fold more than if no hormones were given[21]. Utilizing half this occurrence rate for women, or 0.163 per cent per year, there were 24 per cent ulcers versus the average expected incidence in this group of about 3.8 per cent, and therefore the rise in risk is about 130-fold.

The etiology of the higher incidence of peptic ulceration in the steroid-treated patient is still an unsettled problem. Studies have shown no consistent differences in secretion of hydrochloric acid, uropepsin and gastric mucus in patients before and during steroid hormone therapy. The best evidence to date is that these hormones act by inhibition of local healing of normal ulcerations via two mechanisms. The first in the case of oral corticosteroids is the high local concentration of the hormone particularly in the stomach. This may account for the much higher incidence of steroid-induced gastric ulcers compared to the spontaneous form (62 per cent in our series compared to about 10-12 per cent normally). The low incidence of peptic ulceration in patients receiving corticotrophin intramuscularly also suggests the importance of these local factors. West and Savage reported a total of 115 cases of rheumatoid arthritis patients treated as long as two and one-half years with daily injections of this hormone[22,23]. No routine roentgenological studies were made of the gastrointestinal tract but only two patients developed symptomatic ulcers. The second mechanism is due to inhibition of healing by circulating hormones as shown by Janowitz and his group in dogs with gastric explants who received both cortisone and ACTH intramuscularly and both inhibited healing of experimentally induced ulcers[24].

Conclusion

Fifty-seven patients, most of whom had systemic *lupus erythematosus* requiring large doses of corticosteroids, had serial upper gastrointestinal x-rays

performed at intervals of three months. An additional 20 patients had one examination. The incidence of peptic ulcer in 41 of these who were treated with salicylates and antimalarials was five per cent. Seventeen patients, or 27 per cent of the steroid-treated group, developed peptic ulcers. Five of the 12 treated males in the series, or 41 per cent, showed these changes, and 24 per cent of the female patients.

In 16 cases where definite ulcer craters were found, 10 were gastric in location and six duodenal. The occurrence of ulceration was directly proportional to the dosage of corticosteroid employed. There was no statistically significant difference in incidence of ulceration between prednisone, prednisolone, methylprednisolone, triamcinolone or dexmethasone. Converting the dosage of steroids utilized to prednisone equivalents, the incidence ranges from the occurrence of no peptic ulcers below 10 mg. per day, four to 23 per cent from 10 to 59 mg. per day, and 47 per cent when the dosage was over 60 mg. per day for two months or more. Four patients who developed ulcers had been on a prophylactic ulcer regimen. One of them had a deformed duodenal bulb and ulcer symptoms at the start of therapy and the other three received the highest doses of the steroids, namely 100 mg. per day of prednisone, 96 mg. per day of triamcinolone and 144 mg. per day of methylprednisolone.

Ulcer symptoms were present in 12 of the 17 patients with lesions. Two others were psychotic. Two additional patients had their ulcer craters appear and fully heal without symptoms, change in steroid therapy or ulcer regimen. One ulcer healed with only reduction in steroid dosage.

A total of 28 patients, of 63 given corticosteroids, had ulcer symptoms while taking the newer hormone, and 12 of the symptomatic cases developed proven peptic ulcers. Consequently complaints of dyspepsia during steroid therapy should be given serious consideration and a full ulcer regimen begun.

During the period in which the patient receives steroid therapy, the chances of developing peptic ulcer are 100 to 130 times greater than for the nonsteroid-treated patient. The only preventive method is the use of prophylactic ulcer regimens with antacids and anticholinergic therapy in patients receiving 10 mg. per day of prednisteroids, or its equivalent. All patients with an ulcer history or those who develop dyspepsia on steroids should be placed on a regular ulcer schedule regardless of steroid or dose employed.

Addendum

Additional data has been obtained on dexamethasone treated patients. A total of 27 have received 58 upper gastrointestinal x-rays while receiving this hormone. Fourteen had base line studies immediately prior to the institution of dexamethasone therapy and every few months during it. The other 13 patients had examinations performed at intervals of several months while receiving this

hormone with the exception noted below. Only one patient who had an ulcer history was placed on a prophylactic ulcer regimen (E.M. Table V). A recurrent ulcer was noted after seven months of older corticoids and 11 months of dexamethasone. She had been receiving 1.0 mg. per day for two months prior to the last x-ray. A total of six new ulcers were induced by the use of doses varying from 1.0 to 20.0 mg. per day for periods of as short as two months to as long as 18 months of steroid therapy. All the ulcers were symptomatic. A total of 11 patients who received dexamethasone had epigastric distress and had routine x-rays throughout their course of therapy. Five of these had demonstrable peptic ulcers; four were located in the antrum of the stomach and one in the duodenum. An additional patient (S.S. Table V) had repeated hematemesis and three normal x-ray studies. Her symptoms disappeared after institution of a vigorous ulcer regimen and a change to parenteral hydrocortisone.

Four of the six ulcers appeared on doses of 2.25 mg. per day or more of this steroid. The dose ulcer relationship and 22 per cent incidence in the dexamethasone group is essentially similar to that produced by the other corticosteroids studied.

In order to avoid the effect of prolonged local concentrations of corticosteroids, it may be advisable to give these hormones immediately before meals, so that the material leaves the stomach as soon as possible rather than employ the usual practice of administration after meals or with a small amount of food.

If a serious ulcer problem or intractable epigastric distress should appear, parenteral administration of the coritcoids usually completely relieves the symptoms and aids healing. Once the ulcer is healed, the patient may be able to tolerate small doses of oral steroids.

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THE OMINOUS RECIPROCITY BETWEEN LIVER DISEASE AND PANCREATITIS*

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A relationship between the liver and pancreas has been generally accepted because of the proximity of the two organs, their interrelated drainage of venous blood and drainage of excretory substances (bile and pancreatic juice respectively) through a common opening–the papilla of Vater.

Both morphologic and functional changes in the pancreas of patients with liver disease have been documented by various authors who described fibrosis, interstitial inflammation, acinar and ductal dilatation in the former[1,2,3]. While these changes were considered to be due to deficient enzyme secretions, various attempts to correlate these findings with the results of pancreatic enzyme studies have not been successful inasmuch as the enzymes vary in different patients and are frequently normal or increased in patients with either acute or chronic liver disease[4,5,6].

Changes in the liver of patients with pancreatic disease have also been described. Thus, many reports are found in which pancreatic lithiasis has been considered the cause of fatty metamorphosis–hepatomegaly, jaundice and ascites and even cirrhosis[7,8,9]. Similar changes have been noted in cases of acute pancreatitis, chronic relapsing pancreatitis, cystic fibrosis and even carcinoma of the pancreas[10-14]. Some attempted to explain these hepatic changes as being caused by interference with hydrolysis and absorption of proteins, amino acids, fats and vitamins and possibly choline. Others considered the release of toxic substances from necrotic pancreatic tissue as the cause of liver damage. In addition to the toxic effects on the liver, pancreatic lesions may also cause jaundice and secondary liver cell damage by mechanical compression of the bile ducts.

Pancreatic disease may produce pathologic changes in the liver both by disturbances in the exocrine, as well as the endocrine function of the pancreas, "dysinsulinism" being the main effect in the latter.

Insulin is considered to be necessary for many of the glycogenic and glycogenolytic processes in the liver, for the regulation of the glucose output from the liver, for stimulation of hepatic lipogenesis, for inhibition of ketone body formation, for acceleration of the rate of protein synthesis and/or incorporation of amino acids into protein. Hence, disturbances in the insulin metabolism may

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.

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produce many changes. Hepatic functional and structural abnormalities, however, vary greatly in different groups of diabetic patients, and depend on the control of diabetes. Bromsulfalein retention is the most common abnormality seen in about 50 per cent of the cases depending on the severity and complications of diabetes—i.e. amount of fat in the liver. The flocculation tests are abnormal in only about 20 to 25 per cent. Urobilinogenuria and bilirubinuria appear in some cases[1].

Hepatomegaly appears in about half of the diabetics—especially the young ones. Histologically, the most characteristic finding is the presence of vacuoles in the nuclei of the hepatic cells of these large livers. The Kupfer cells may be large and contain much Vitamin A. The cytoplasm may show fine vacuolization due to glycogen.

Fatty liver is not an uncommon finding and may even be a cause of death in diabetics. It is found more in cases with acidosis and coma. The amount of fat is greater in those with insulin insensitivity. Hemosiderin pigment too is frequently found in fatty livers.

Although cirrhosis is rare in nonalcoholic diabetics, it is more common in them than in nondiabetics. If present, however, it may also be due to associated causes—e.g., alcoholism, hepatitis and cardiac failure.

While it is agreed that a pathologic process in either organ (liver or pancreas) may adversely influence the structure and function of the other organ, there are certain conditions which seem to affect both organs simultaneously, one possibly more manifestly than the other. Thus, simultaneous injury to the liver and pancreas may occur in viral and toxic hepatitis[15,16], mumps[17], infectious mononucleosis[18], hemochromatosis, vascular lesions *(periarteritis nodosa)*, alcoholism[19], and malnutrition (chiefly protein deficiencies)[20]. Dietary protein deficiency from any cause leads to a decrease of proteins for enzyme precursors with resultant fatty infiltration and decreased enzyme formation which in turn leads to decreased amino acid absorption and more fatty changes. At times fatty changes appear first in the pancreas before they are noted in the liver[21] and the pancreatic deficiency then seems to aggravate and perpetuate the hepatic damage. Other times the changes following malnutrition appear simultaneously and increase in severity as the condition continues[20].

We became interested in this ominous reciprocal interrelationship between the liver and pancreas when we observed the more dramatic course—usually downhill—of patients in whom both organs were damaged.

In the past few years we have encountered a number of patients who entered the hospital under the picture of hepatitis, cirrhosis or acute abdominal disease and in whom later the presence of both pancreatic and hepatic damage was established. These patients had a stormier clinical course and the group had a higher mortality rate than other cases with similar findings but without interrrelated pathologic findings.

All of these patients, while originally presenting the clinical picture commonly associated with their admitting diagnosis, had more abnormalities in the results of their laboratory tests (Table I), were very ill and continued mostly on a downhill course. The various therapeutic procedures usually used in patients with hepatitis had no or little influence on these cases. In most of them the possibility of an associated pancreatitis was not even entertained and the patient was mainly considered a severe case of hepatitis—viral or toxic—so that in some of them determination of amylase was omitted. The finding of icterus in cases of pancreatitis did more often direct the examiner's thinking to an associated liver condition.

Because of these observations, the thought occurred to us that the critical condition of these patients was due to the fact that only one part of their illness was treated and one part was ignored, i.e., we were treating the liver disease and ignoring the pancreatic condition or treating the manifesting pancreatic disease and ignoring the liver damage, all because of the monoetiologic concept of the patient's illness.

The profound pathologic changes seen in both the liver and the pancreas of some of the patients of our group can readily explain the abnormal results of the physical examination and the laboratory tests. They can also explain the grave clinical picture presented by some of them and at the same time invite some improved plan of therapy in similar cases.

Comment

As stated above, changes in the pancreas in diseases of the liver and vice versa have been noted. The significance of these changes, however, has not been fully stressed in the management of patients suffering from disease in either organ, or even from conditions which affect both organs simultaneously. Thus, unless patients with pancreatic disease manifest extensive changes, e.g., jaundice, hepatomegaly, splenomegaly and ascites, a liver involvement is rarely considered. Yet, beneficial results of vitamins and pancreatic extracts, diet (low fat, high protein, high carbohydrate) and diuretics in some cases of fatty liver secondary to pancreatic disease are seen. This is, of course, important since, if not treated, some of these fatty livers might go on into cirrhosis. Moreover, whether the fatty liver or cirrhosis is due solely to the pancreatic disease rather than to alcoholism or poor dietary intake, as frequently present in these cases, is of no importance. The important point is that these patients do have both conditions and should be treated accordingly.

The need for diagnosing and treating hepatic damage in cases of pancreatic disease has been stressed by Lucas and Best[22], by Cole and co-workers[23] who described a pancreaticohepatic syndrome and by Gillman[20], who thought that severe malnutrition with hepatic lesions preceded the lesions in the pancreas. Sanes[8] too believed that there appears to be in some cases a fundamental rela-

TABLE I

No.	Age	Sex	Race	Diagnosis	Alcoholic history	Diarrhea	Weight loss	Liver x	Spleen x	Abdominal tenderness	Ascites	Fever	Abnormal hep. function test	Icterus	Anemia	Amylase	Course	Biopsy postmortem surgery
1.	60	F	W	Cirrhosis	20 yrs.	0	+	4	1	+	+	0	+	+	0	—	Died	B—Cirrhosis
2.	51	F	W	Cirrhosis	—	0	+	?	?	+	+	+	+	+	0	—	Died	P—Cirrhosis and pancreatitis
3.	43	F	W	Cirrhosis	—	0	+	5	2	0	+	+	+	+	mild	—	Died	P—Cirrhosis and pancreatitis
4.	38	F	W	Acute abdom.	5	+	+	?	?	+	0	+	±	mild	0	S-532 U-512	Imp.	B—Fatty liver Acute pancreatitis
5.	38	M	C	Acute gastritis	+	0	+	0	0	+	0	0	+	+	0	S-128	Imp.	B—Cirrhosis
6.	42	M	W	Acute hepatitis	+	+	+	4	0	+	±	+	+	+	0	S-36, 147,50 320		B—Cirrhosis S—Chronic pancreatitis
7.	24	F	W	Anemia purpura	?	0	+	1	3	0	0	+	±	+	+	—	Died	Secondary hemachromatosis
8.	65	M	C	Anemia	?	0	+	4	3	0	0	+	±	+	+	—	Died	Secondary hemachromatosis
9.	44	F	C	Acute gallbladder	?	?	+	?	?	0	0	+	+	+	+	—	Died	Fatty liver Chronic pancreatitis
10.	45	M	C	Liver damage	mod.	+	+	7	2	+	0	+	+	+	+	—	Died	Tbc. toxic hepatitis Acute pancreatitis
11.	41	M	C	Purpura	?	0	+	1	0	+	0	+	+	+	+	—	Died	P. C. thrombosis Cirrhosis and pancreatitis
12.	30	F	W	Gallbladder dis.	+	0	+	3	1	+	0	+	+	+	+	—	Died	Intrahepatic chol. pancreatitis
13.	65	M	W	Penetrating ulcer?	+	0	20	2	0	0	0	0	+	+	0	—	Died	Pancr., Ca. of pancreas, cirrhosis
14.	50	M	C	Alcoholism	+	0	10	2	0	0	0	0	+	+	0	—	Died	Pancr., Ca. of pancreas, cirrhosis
15.	65	M	W	Coma	?	0	?	0	0	0	0	+	0	0	0	—	Died	Diabetic coma, Chronic relapsing pancreatitis
16.	42	F	C	Coma	+	+	+	4	0	0	0	+	+	+	0	—	Died	Toxic hepatitis
17.	41	M	W	Peptic ulcer	+	±	20	2	0	+	0	+	+	+	+	16	Died	Fatty liver Chronic cirrhosis
18.	45	M	C	Heroin addict	+	0	?	2	1	0	0	+	+	0	0	—	Imp.	Cirrhosis and pancreatitis
19.	48	M	C	Cirrhosis	+	0	+	1	0	+	+	+	+	+	mild	64	Imp.	B—Cirrhosis
20.	69	M	W	Cirrhosis	+	0	+	8	0	+	0	+	+	+	0	—	Imp.	B—Cirrhosis

tion between the pancreas and the liver in fat metabolism, apparently dependent on an enzymatic basis in protein and lecithin digestion or, perhaps, on a "hormonal" basis and that for these cases the use of the term "pancreaticohepatic syndrome" in a strict and conclusive sense is justified.

The damaging pancreatic influence on the liver is also supported by a survey of 139 diabetics, by Frankel et al[24], 46 of whom had abnormal hepatic function tests and in 18 of whom no other possible factor could be found.

Although a hepatic factor is given in the etiology of pancreatitis, this factor seems to be ignored most of the time when dealing with cases of hepatitis, as evident from clinical reports and our own series. This may partly be due to the fact that the results of enzyme determinations, on which the diagnosis of pancreatitis is based, vary greatly. Thus, Cummins and Bockus[25] and Crandall and Cherry found increased concentrations of amylase in 20 to 23 per cent of their cases of hepatitis and cirrhosis respectively, while the lipase was increased in about 33 per cent. On the other hand, Lagerlof[26] found increased lipase in only one of 24 patients with hepatitis, while Comfort and associates[27] observed high lipase values in 4 of 17 cases of hepatitis. Cummins and Bockus[25] moreover stressed the poor prognosis of hyperlipasemia in that three of six hepatitis cases with high lipase values died. Thus, the hyperenzymemia in cases of hepatitis should be considered as an expression of an association of hepatic and pancreatic disease and the patient managed accordingly. In support of this one might mention Neefe's[28] observation that in volunteers who developed hepatitis, sometimes the early symptoms were indistinguishable from acute pancreatitis with occasional severe epigastric pain radiating to the back and elevated amylase and lipase values in the blood.

While in some of the cases reported and in our cases too, no estimations of pancreatic enzymes by duodenal drainage and no studies of the stool were done to support pancreatic damage, postmortem findings or surgical findings showed lesions of various degrees in the pancreas. Whether the presence of fatty changes in the liver were on the basis of pancreatic disease (including diabetes) or independently associated with restricted diet, ingestion of alcohol, intestinal infections or disease (ulcerative colitis, jejunocolic fistula) etc., their presence is of clinical importance. Moreover, even if the hepatic changes were instigated by other causes—alcoholism, dietary deficiency, diabetes, infection—the pancreatic factor may still have accentuated them and may have prevented their improvement and eventual disappearance by interfering with the liberation of lipotropic factors.

For the present the problem lies first in the awareness and clinical recognition of this interrelationship, and secondly in the development of some plan of management of these cases. Thus, first every patient with severe acute hepatitis or cirrhosis should be checked for the presence of pancreatic disease and every case of pancreatitis should be investigated for a possible liver in-

volvement. Secondly, these patients must be treated as having two distinct entities—disease of the liver and disease of the pancreas. All therapeutic procedures used for patients suffering from either liver or pancreatic disease must be used in these cases as a combined procedure, so as to ameliorate the changes produced by both conditions.

The symptomatology in some of these cases is not only one of simple addition—symptoms from liver plus pancreas—but of cumulative progression since one diseased organ may produce substances which affect adversely the other diseased organ, thus multiplying the number and severity of symptoms. The treatment, therefore, must be intensive and prompt so as to interrupt as soon as possible the pernicious reciprocal intoxication and tissue destruction. As in every instance of combined therapy, the effects and side-effects of the various therapeutically used substances must be carefully weighed so as not to aggravate some of the presenting symptoms. The indications for intravenous glucose, insulin, steroids, vitamins, antibiotics, electrolytes, blood or blood substitutes, and their respective amounts used must be checked against the predominance of the respective organ symptoms. Fortunately, in most cases, the applied therapeutic procedures are beneficial for both conditions so that only few specific items must be considered. Thus, continuous gastric aspiration and anticholinergic drugs are of great value in acute pancreatitis but are not needed in hepatitis. Insulin is needed in some cases of pancreatitis because of the hyperglycemia but must be used with caution in hepatitis because of the need for a more than normal sugar level in hepatic cases. Antibiotics must be given in pancreatitis, but are not usually needed in acute hepatitis. Blood and/or blood substitutes—plasma, albumin or dextran—are frequently urgently needed in pancreatitis, but not in hepatitis. The electrolytes, sodium, chloride, potassium and calcium, are earlier disturbed in pancreatitis and must be carefully replenished. Finally, while the indications for steroids are debatable, they are often of more value in early cases of pancreatitis than hepatitis.

In conclusion, attention is directed to the ominous reciprocal relationship between liver and pancreas which should be suspected in every case which presents itself under the picture of a severe hepatitis or pancreatitis. A history of diabetes or gallbladder disease in a patient coming under our observation as a case of hepatitis or cirrhosis should alert us to this possibility. Patients with this condition are gravely ill, and have a more serious course, frequently terminating fatally. Combined therapy, i.e. therapy directed to both damaged organs, must be instituted to get better therapeutic results.

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FURTHER EXPERIENCE WITH HEMAGGLUTINATION IN VIRAL HEPATITIS*

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Recent studies by the authors[1-4], confirmed by Rubin, Kemp, and Bennett[5], Havens[6] and McCollum et al[7] have demonstrated the hemagglutination reaction in viral hepatitis to be of significant clinical value.

This procedure consists of testing the reaction of erythrocytes from the macacus rhesus monkey against human viral hepatitis serum. The following describes further experiences with this hemagglutination test over the past four years in 1,710 individuals and patients.

Method

Macacus rhesus monkey red blood cells were collected in A.C.D. solution and stored in the refrigerator. A working suspension was prepared by washing the cells 3 times in 0.9 per cent NaCl solution, resuspending them after the last washing to make up a 1 per cent suspension by volume. The working suspension is made up just before using, and unused portions are discarded. The cells stored in A.C.D. solution gradually lose their sensitivity and should not be used after 10 days' storage. Two-fold serial dilutions of the patient's serum in 0.2 ml. volume were made in plastic disposable trays to which were added equal volumes of the 1 per cent suspension of red blood cells from the monkey. The serum dilution was incubated for one hour at 37° C. The trays were shaken gently to dislodge the button of sedimented erythrocytes and cells were examined by transmitted light for the presence of clumping. In a negative test the cells can be suspended by gentle agitation into a smooth, homogeneous suspension. A positive reaction is indicated by the presence of large to small clumps

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.
Supported by United States Public Health Service Grant #E1747, NIH, Bethesda, Maryland and the American Cancer Society Grant #1743.
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of cells in the fluid medium. In cases of doubtful positive reactions, it was found that repeating the reading within 20 to 30 minutes will often eliminate false or doubtful positive reactions. The end point was considered to be the highest dilution of serum in which a definite agglutination was macroscopically visible.

The conventional scoring was used in the readings and is described below:

4+ the cells are welded into one solid mass

3+ there are several large, irregular clumps with numerous small aggregates

2+ the clumps are moderately large and uniform in size and distribution

1+ there is a granular appearance, due to the presence of small clumps of cells

± there is a very finely granular appearance, due to the presence of minute clumps of cells. This is read in comparison with the cell control. In testing a series of 125 healthy donors, it was originally found that 110 had titers of less than 1:8, whereas 13 of 18 persons diagnosed as having an acute attack or recent episode of viral hepatitis, infectious or homologous serum varieties, had titers of 1:8 or greater. These observations have led us to fix the value of 1:8 as the titer which separates normal from elevated readings.

Clinical Material

The blood sera of patients and individuals tested were collected from various hospitals, blood bank centers, private physicians, and the United States Public Health Service Infectious Unit, Chamblee, Georgia (Dr. Gerald Cooper, Director). Included in this series are 8 groups of patients. The first six groups, A-F inclusive, include patients and subjects studied during the first three years of experience with the hemagglutination phenomenon in viral hepatitis. Groups G and H include cases studied over an additional period of one year.

Group A:—Four hundred thirty-one medical and surgical cases without demonstrable liver pathology but with extrahepatic primary diseases such as myocardial infarction, hypertensive cardiovascular disease, cerebral thrombosis, peptic ulcer, diverticulitis, and fracture cases. These patients acted as "controls". Nine additional cases of poliomyelitis and five cases of acute influenza were also studied.

Groups B and C:—Thirty-six viral hepatitis patients were studied of whom 22 were acute (Group B) and 14 were chronic (Group C). These consisted of both infectious (IH) and homologous serum (SH) varieties. The 36 cases of both types of virus hepatitis were diagnosed by combinations of 2 or more of

the following: autopsy, liver punch biopsy, abdominal laparotomy, the clinical findings of virus hepatitis as evidenced by jaundice, hepatomegaly, and characteristic "profile" of the battery of liver function tests. Numerous cases of viral hepatitis and other blood sera were supplied through the courtesy and cooperation of various colleagues in hospitals of Los Angeles and other cities. The sera were kept in the frozen state until ready for testing.

Group D:—Tests were done on 21 patients with jaundice. They were proved by autopsy, laparotomy, or liver punch biopsy to have either metastatic carcinoma of the liver, choledocholithiasis, cholelithiasis with cholecystitis, Laennec's or biliary cirrhosis of the liver, carcinoma of the pancreas, or obstructive hyperplasia of the sphincter of Oddi.

Group E:—Twenty patients studied during and immediately after an epidemic of infectious hepatitis occurring at a college in Pomona, Calif.

Group F:—One hundred twenty cases of nonjaundiced forms of viral hepatitis studied during an outbreak of infectious hepatitis in West Los Angeles officially reported by the Los Angeles City Health Department.

Group G:—One thousand seventy-three miscellaneous sera were tested. Four hundred fifty-one were psychiatric patients from mental institutions, 621 from the authors, and 3 from the Metropolitan State Hospital (for psychiatric cases), two of which proved to be chlorpromazine poisoning.

Group H:—Nine sera from the Pediatric Division of Bellevue Hospital, Division of New York University were tested.

Results

One thousand three hundred thirty-four subjects were screened as "controls" comprising 60 normal individuals, 52 (87 per cent) negative, and 8 (13 per cent) positive; 823 patients with illnesses other than biliary tract or infectious in character, 720 (87 per cent) negative, and 103 (13 per cent) positive; 451 psychiatric cases from mental institutions, 365 (81 per cent) negative, and 86 (19 per cent) positive.

Ninety-five patients were studied with the jaundiced form of acute viral hepatitis; the diagnosis was demonstrated by the clinical findings in each case of jaundice with either hepatomegaly or painful, tender liver, plus typical laboratory findings such as bilirubinemia, strong positive thymol turbidity and cephalin flocculation tests. Of these, 9 patients gave positive reactions, or 10 per cent. Eighty-six cases gave positive reactions, or 90 per cent. Both the infectious and homologous serum varieties of hepatitis are represented in this group of patients.

One hundred twenty cases of acute nonicteric hepatitis, as demonstrated by hepatomegaly and/or painful, tender liver with strongly positive thymol turbidity test plus strongly positive cephalin flocculation tests (3+ or 4+) in addition to positive hemagglutination tests for viral hepatitis, gave results of 42 (35 per cent) negative and 78 (65 per cent) positive. These cases were studied during an epidemic of icteric, acute viral hepatitis as reported by the Los Angeles City Health Department[4]. Seventy-six additional cases of acute nonicteric viral hepatitis gave results of 12 (16 per cent) negative and 64 (84 per cent) positive. In the 95 cases of acute icteric viral hepatitis, tests were made on 2 or more occasions in 78 patients, or 82 per cent of cases.

TABLE I

REACTIONS OF VARIOUS SERA WITH MACACUS RHESUS ERYTHROCYTES

Group	No. of cases	Positive Titer of 1:8 or greater	Negative Titer of less than 1:8
I Control	1334	197 cases 15%	1137 cases 85%
II Obstructive jaundice nonviral	40	2 cases 5%*	38 cases 95%
III Acute viral hepatitis	291	228 cases 78%	63 cases 22%
a. Jaundiced	95	86 cases 91%**	9 cases 9%
b. Nonjaundiced	196	142 cases 72%***	54 cases 28%

*With the exception of these 2 cases, all other cases in this group were negative in each instance in two or more tests performed during the illness.
**Positive test at least once in multiple tests performed in each of 78 of these patients during the illness.
***Positive test at least once in multiple tests performed in each of 72 of these patients during the illness.

In the 120 cases of acute, nonicteric viral hepatitis, multiple tests were made during the course of illness in 74 patients or 62 per cent of cases.

If only one sampling were considered, the incidence of the hemagglutination reaction would have been less than that reported in the foregoing figures; negative or borderline positive reactions noted early in the course of illness in some cases became positive at a subsequent blood sampling. As in the case of other liver function tests it is desirable to test for hemagglutination on more than one occasion and preferably in a serial manner.

Twenty cases of infectious mononucleosis with positive heterophile reactions were tested. Thirteen (65 per cent) gave negative results. Seven (35 per cent) gave positive results.

In a group of 40 patients with nonviral types of janudice due to extrahepatocellular, intra- or extrahepatic obstructive jaundice, 38 gave negative hemagglutination tests for viral hepatitis. Two cases gave positive reactions. These were in 2 newborn infants, whose sera were supplied through the courtesy of Dr. Saul Krugman, from the Pediatric Division of Bellevue Hospital, Division of New York University. Both of these infants were found at autopsy to have congenital atresia of the bile ducts. All the other cases in this group were adults and are the subject of a separate communication. Havens[6] has recently reported 100 per cent diagnostic accuracy with a hemagglutination reaction for viral hepatitis in a series of 23 patients with obstructive, nonviral jaundice. This observation confirmed our original report in a group sampling of similar size[2]. Our series of patients revealed a 95 per cent accuracy in the diagnosis of nonviral, obstructive jaundice; however, in the group of 38 adult cases of obstructive jaundice, hemagglutination was absent in each case, or 100 per cent. McCollum et al[7], have also recently confirmed these findings.

In the group of infants, 2 of the 9 cases of jaundice gave positive reactions (titers of 1:8 or higher) where congenital biliary obstruction was present. An additional 2 cases gave negative reactions, one of which was diagnosed by liver function tests as viral hepatitis through maternal transmission. Five of the remaining gave positive hemagglutination tests in infants diagnosed as viral hepatitis.

Comment

These cases lend additional evidence to the value of further studies of the nature of the hemagglutination reaction in viral hepatitis. At present, it is not possible to determine whether the phenomenon concerned results from the direct action of the virus upon the erythrocytes, or from the activity of viral antibodies, or from the presence of some abnormal blood component occurring during the course of the hepatitis.

Attempts at screening viral hepatitis carriers in blood donors are at present being conducted by Rubin, Kemp, and Bennett[5]. Preliminary impressions by these authors have recently indicated that the hemagglutination reaction may be valuable in predicting viral hepatitis carriers.

Positive findings in 7 or 35 per cent of 20 cases of infectious mononucleosis in Group G lend support to the concept of hepatitis as a concomitant complication in a significant percentage of cases of infectious mononucleosis. Infectious mononucleosis is regarded by most authorities as viral in etiology, although as in the case of hepatitis of viral origin, the virus has not been isolated to date.

Summary and Conclusion

1. The blood sera of 1,710 cases were studied for a hemagglutination reaction previously noted in both infectious and homologous serum varieties of viral hepatitis over a 4-year period.

2. The hemagglutination reaction involved concerned the reactivity of macacus rhesus monkey erythrocytes against human sera of patients with viral hepatitis.

3. Two hundred ninety-one cases with acute viral hepatitis gave the following results: of 95 jaundiced patients, 9 (10 per cent) gave a negative reading and 86 (90 per cent) gave positive results; of 196 nonicteric patients, 54 (28 per cent) gave negative results, and 142 (72 per cent) gave positive results.

4. One thousand one hundred thirty-seven cases of "controls" in a total of 1,334 cases, or 85 per cent, were negative. One hundred ninety-seven cases (15 per cent) gave positive results.

5. The test was negative in 38 out of 40 cases of nonviral obstructive jaundice, or 95 per cent diagnostically accurate in a series of adult and infant cases.

6. In 38 cases of obstructive jaundice in adults, no hemagglutination occurred, giving 100 per cent accuracy in this age group.

7. These observations warrant further investigation into the nature of the hemagglutination phenomenon in viral hepatitis.

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A COMPARATIVE STUDY OF HYDROCHLOROTHIAZIDE AND CHLOROTHIAZIDE ON BLOOD AMMONIA AND ELECTROLYTE BALANCE IN CIRRHOTIC PATIENTS*

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Hydrochlorothiazide is the recently produced 3,4 dihydro-derivative of chlorothiazide which, in animal experiments, has been shown to be 7 to 16 times more potent on a mg. for mg. basis than chlorothiazide with regard to sodium excretion[1]. The two compounds differ structurally in that hydrochlorothiazide has no double bond in the heterocyclic ring (Fig. 1). Both are similar in other respects and are similar to acetazolamide in that all three contain the sulfonamide radical and are thus representatives of the heterocyclic sulfonamides which have been shown to be inhibitors of carbonic anhydrase *in vitro*[2]. Thus, chlorothiazide has been shown to be 1/25th as potent as acetazolamide in this regard[3] while hydrochlorothiazide has been shown to be 1/9th as potent as chlorothiazide in its anticarbonic anhydrase activity[1].

In vivo, however, chlorothiazide has been shown to partake not only of the properties of a carbonic anhydrase inhibitor, but also of the mercurial diuretics being closer to the latter in its diuretic effects[4]. With less carbonic anhydrase inhibition as found in hydrochlorothiazide we may expect more of the mercurial-like effects and accordingly, in dog experiments the chloride ion has been shown to be the principle one excreted with hydrochlorothiazide.

The present study was undertaken to compare in humans the excretion patterns obtained with hydrochlorothiazide and chlorothiazide at their optimum dosage. In addition, because of previous reports linking the administration of chlorothiazide to cirrhotic patients with increases in blood ammonia with and without increases in encephalopathy[5,6,7], a comparative study of the two drugs in such patients was undertaken. Furthermore, because of previous studies suggesting an increase in cerebral uptake of ammonia at higher pH levels[8,9], blood pH was measured simultaneously with the blood ammonia levels.

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*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.

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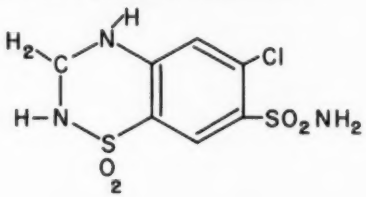
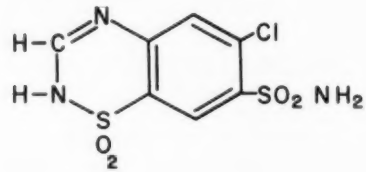
Materials and Methods

A normal, nonedematous male on free dietary intake was given hydrochlorothiazide in increasing dosage from 25 mg. through 200 mg. at weekly intervals. Urines were collected every two hours in the postabsorptive state from 6 a.m. to 6 p.m. The drug was given after the initial two-hour period which served as the control as did one day without drug. Two hundred fifty c.c. of distilled water were given prior to each two-hour period. Measurements of

HYDROCHLOROTHIAZIDE



CHLOROTHIAZIDE



ACETAZOLEAMIDE
(DIAMOX)

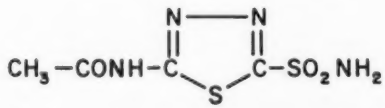


Fig. 1—Formulas of three representative heterocyclic sulfonamide diuretics.

urinary pH, titrable acidity, bicarbonate, and ammonia were made within 15 minutes after collection. Sodium, chloride, potassium, and osmolality were measured on each two-hour specimen.

Three additional excretion studies were carried out as described using a 50 mg. dose of hydrochlorothiazide. The averages of these 3 studies were compared with similarly obtained averages of 3 excretion studies using a 500 mg. dose of chlorothiazide.

Five cirrhotic patients were placed on controlled dietary intake. None had evidence of renal disease as noted by serum creatinine levels or by repeated urinalyses. Venous and arterial blood ammonias were drawn within a few minutes of each other from the medial subcutaneous antecubital vein and the femoral artery, respectively, one to two hours after breakfast. Twenty-four hour urine collections were measured for sodium, chloride, and potassium; serum electrolyte levels were followed two to three times weekly.

Methods

Sodium and potassium levels were measured by the Baird internal standard flame photometer. Urinary ammonia was measured by the microchemical method

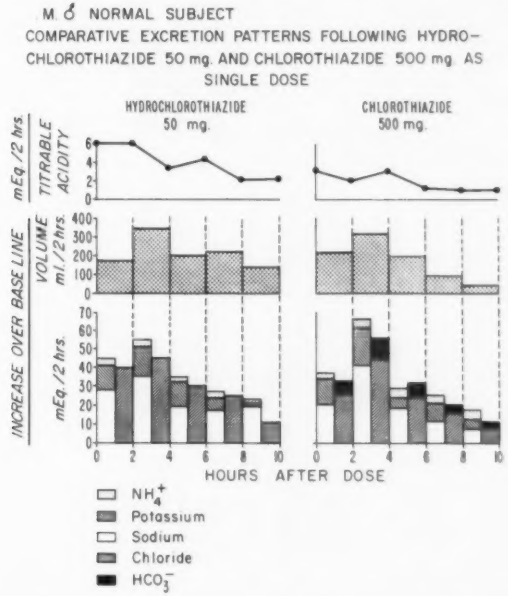


Fig. 2—Urinary excretion patterns following optimal doses of hydrochlorothiazide and chlorothiazide compared. Values are for increase over base line per two-hour period after each drug.

of Folin and MacCullem[10]; titrable acidity was determined by titration to pH 7.4 with N/10 sodium hydroxide; chloride was measured by colorimetric titration with mercuric nitrate[11]; bicarbonate was determined both in urine and serum by back titration after the addition of N/10 nitric acid[12]. Blood ammonia was measured by the Seligson modification of the Conway method[13]; blood pH was determined on a MacBeth pH meter, and osmolality was measured in urine samples using a Fiske osmometer.

Results

It was found that the optimum dosage of hydrochlorothiazide lies between 50 and 100 mg. and that doubling the dose above 50 mg. is not followed by any significant increase in the excretion of sodium and chloride, although an increase in the excretion of potassium and bicarbonate is noted at the 200 mg. dose. Thus, the carbonic anhydrase inhibition of hydrochlorothiazide becomes manifest with greater dosage. Urinary osmolality follows the same pattern as does the electrolyte excretion values at all doses. There thus seems to be no direct blocking effect on water re-absorption by hydrochlorothiazide at any of the doses tested.

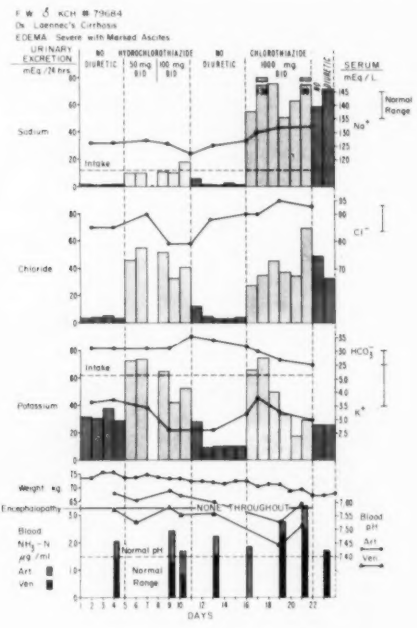


Fig. 3

Figure 2 demonstrates that the times of onset and of maximum diuresis are similar when hydrochlorothiazide and chlorothiazide are compared in the manner described. Sodium, chloride, potassium, and ammonia excretion are approximately equal with both drugs. The ratio of chloride to sodium output during each two-hour period with each drug is also roughly the same. There appears to be a longer duration of activity with hydrochlorothiazide than with chlorothiazide as the increase in sodium excretion continues at levels significantly higher than base line for the ten hours of the study with hydrochlorothiazide, while it falls to near base line levels with chlorothiazide by this time.

The outstanding difference between the two drugs appears to be an increase in bicarbonate excretion with chlorothiazide compared to hydrochlorothiazide and a more alkaline urine as seen by the low titrable acidity at the top of the figure. This is probably related to the greater carbonic anhydrase inhibiting activity of chlorothiazide compared to hydrochlorothiazide.

Comparative Studies in Cirrhotic Patients

Case 1:—F. W., a cirrhotic patient with marked edema and ascites had previously become comatose and developed a flapping tremor after three days of chlorothiazide administration. In Figure 3 we note a small rise in sodium

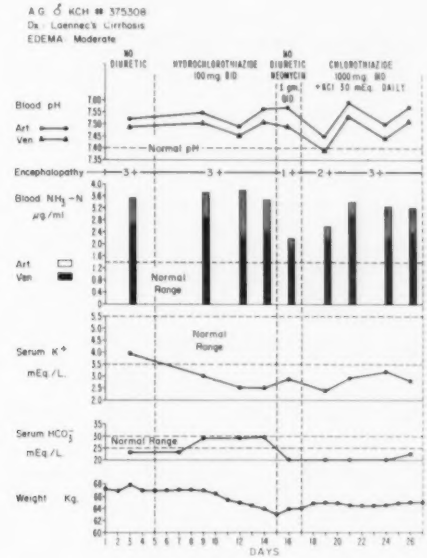


Fig. 4

excretion and a larger rise in chloride and potassium over base line with hydrochlorothiazide. Sodium excretion with chlorothiazide is much greater at 1,000 mg. twice daily as compared to hydrochlorothiazide at 50 and 100 mg. twice a day; and sodium appears to be the predominant ion excreted with the former drug, while chloride appears to be the predominant ion excreted with hydrochlorothiazide. There is a slow falling off of excretion of all electrolytes when chlorothiazide is stopped suggesting that we may have started a diuretic phase with this drug. Total excretion of chloride and potassium are approximately the same with both drugs. Why this patient is refractory to sodium diuresis with one drug and not with another is not clear at present.

Serum electrolyte values show a greater lowering of chloride and a greater rise of bicarbonate with hydrochlorothiazide compared to chlorothiazide. Serum potassium falls with both drugs to markedly low levels.

Blood pH is alkalotic throughout with a drop towards normal early in treatment and a rise towards the end of the six-day period with both drugs, being more accentuated with chlorothiazide. Changes in blood pH are apparently unrelated to changes in blood ammonia, and they also bear no constant relationship to changes in serum bicarbonate.

Blood ammonia is not elevated significantly with hydrochlorothiazide, while with chlorothiazide there is a constant rise with continuous treatment; and at

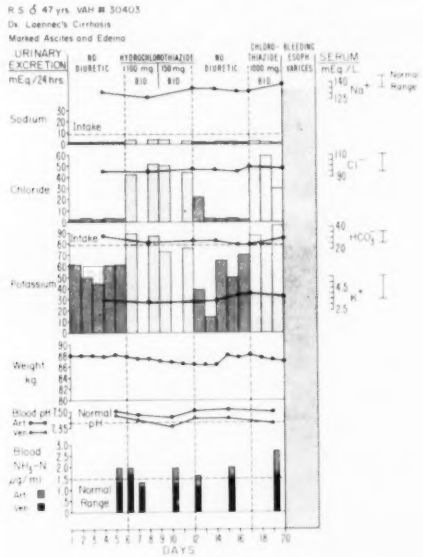


Fig. 5

the end of six days, both arterial and venous levels have reached significantly greater heights than base line values. It is of interest that there are no signs of encephalopathy at higher levels of blood ammonia and that the blood pH levels are lowered simultaneously. This is in accordance with previous findings suggesting a lower uptake of blood ammonia by the brain at lower pH levels[8,9]. Thus, less encephalopathy may ensue at lower pH levels.

Case 2:—A. G. (Fig. 4), a cirrhotic patient with moderate edema and ascites showed frequent signs and symptoms including electroencephalographic changes of severe hepatic encephalopathy throughout. Because of recurrent incontinence, 24-hour urines are not recorded. He was given hydrochlorothiazide, 100 mg. twice daily and chlorothiazide 1,000 mg. twice a day, the latter with supple-

mentary potassium chloride because of low serum potassium at the time the drug was started.

We note that the blood pH is again alkalotic throughout although not to the elevated levels seen with the previous patient. Thus, at least in this patient, it would appear that elevation in blood pH alone is not related directly to the degree of encephalopathy.

Blood ammonia, both arterial and venous, shows no significant difference with either drug and is at high levels throughout except during the two-day course with Neomycin treatment. A sharp drop at this time is accompanied by

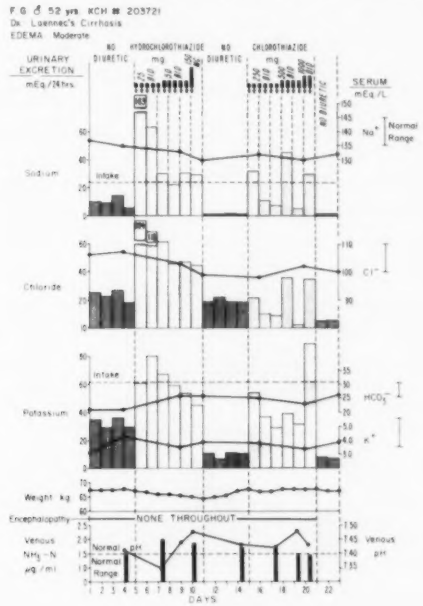


Fig. 6

clearing of the encephalopathy. Thus, a relationship between the levels of blood ammonia and the degree of cerebral toxicity is demonstrated in this patient without any significant change in blood pH occurring simultaneously. Lowering of the blood pH at similarly elevated arterial ammonia levels is not followed by relief of the encephalopathy.

Serum potassium remains at low levels throughout treatment with both drugs. Serum bicarbonate again follows the same pattern seen with the previous patient, a tendency towards a greater rise with hydrochlorothiazide than with chlorothiazide. Again, no constant relationship between serum bicarbonate and blood pH is seen.

Case 3:—R. S., a cirrhotic patient with marked ascites and edema had been resistant to all diuretic therapy previously and as may be seen (Fig. 5), is resistant to sodium diuresis with both hydrochlorothiazide and chlorothiazide. Serum levels of sodium, chloride, and potassium are low throughout without much change during treatment.

Blood pH levels are again alkalotic throughout although not to the degree seen in the previous two patients. Arterial ammonia levels show a rise by the third day of chlorothiazide treatment although the venous levels do not show a

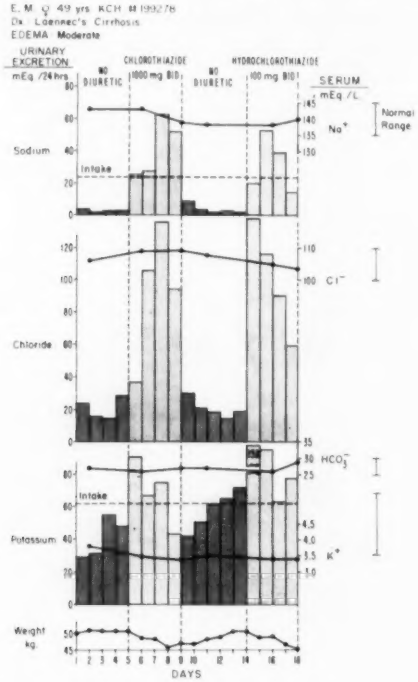


Fig. 7

significant rise over base line with either drug. Arterial levels do not rise above base line with hydrochlorothiazide. Three days after starting chlorothiazide the patient suddenly began bleeding from esophageal varices and the study was stopped.

Case 4:—F. G., a cirrhotic patient with moderate edema shows an immediate rise in urinary excretion of sodium, chloride, and potassium on starting hydrochlorothiazide, 25 mg. daily (Fig. 6). No increase is seen when the dose is doubled or when the 150 mg. is given as a single dose. There is a falling off of diuresis with continued treatment. Chloride is again the predominant ion ex-

creted with hydrochlorothiazide although not so with chlorothiazide. Chlorothiazide, given in a dose equal to 10 times the dose of hydrochlorothiazide was accompanied by a smaller rise in excretion of all measured electrolytes in spite of equal patient weight at the onset of treatment with each drug. The reason for this selective refractoriness to chlorothiazide in contrast to the hydrochlorothiazide refractoriness seen in Case 1 is not clear. Serum values again show a greater fall in chloride and a greater rise in bicarbonate with hydrochlorothiazide compared to chlorothiazide. Lowering of serum potassium is seen with both drugs. Venous pH is again alkalotic with a fall early in treatment and a return to a more alkalotic level with continued treatment. Venous ammonia levels are not significantly affected by either drug and there is no encephalopathy throughout.

Case 5:—E. M., a cirrhotic patient with moderate edema who showed no signs of hepatic encephalopathy at any time. Ammonia levels were not measured and a comparative study of the two drugs during constant intake and for similar periods is shown here (Fig. 7). Chlorothiazide was given first in this case. At 10 times the dosage of hydrochlorothiazide there is an approximately equal excretion of sodium and slightly less excretion of chloride and potassium than with hydrochlorothiazide. The chloride ion is the predominant one excreted with both drugs.

Serum values again show a slightly greater fall of chloride and a greater rise in bicarbonate with hydrochlorothiazide compared to chlorothiazide. Potassium levels are lowered slightly with both drugs. We see a loss of 4½ kg. to 5 kg. with each drug.

Comment

In this small series of cirrhotic patients a few consistencies may be pointed out. 1. With hydrochlorothiazide administration, arterial and venous ammonia levels did not rise significantly in four patients tested while with chlorothiazide, two patients showed a significant rise in arterial ammonia, one of whom also showed a significant rise in the venous ammonia level. 2. Levels of blood ammonia appear to correlate better with the degree of hepatic encephalopathy than do elevations of blood pH (Patient A. G. vs. Patient F. W.). 3. Arterial ammonia levels appear to correlate better with cerebral toxicity than do venous levels. This agrees with findings in several previous studies[14,15]. 4. Arterial levels are consistently elevated above venous levels suggesting the removal of ammonia by the tissues. The increase in arterial levels is not consistently associated with an increased A-V ammonia differences with increases in arterial levels[15]. 5. All of the cirrhotic patients were in alkalosis, and there was no constant relationship between levels of serum bicarbonate and blood pH demonstrating the variability in pCO_2 that may be present in cirrhotic patients. This alkalosis was probably respiratory and not metabolic in nature despite the lack of obvious hyperpnea. There were no precipitating factors to account for a metabolic alkalosis, and

serum bicarbonate levels were not further elevated with either drug. 6. A greater tendency towards hypochloremic alkalosis was noted with hydrochlorothiazide than with chlorothiazide. This effect has also been noted consistently at all dose levels in ten normal subjects given varying doses of hydrochlorothiazide over a three-week period associated with a tendency towards hypokalemia at all doses tried. This portion of the study will be reported upon later.

Chlorothiazide administration has been shown to be followed by elevations in blood ammonia[4,6]. Acetazolamide, a compound structurally and pharmacologically related to chlorothiazide, has also previously been reported to cause increases in blood ammonia[16,17]. In one report[17] there was noted an elevation in arterial and venous ammonia in five of six cirrhotic patients with evidence of pre-coma two hours after the administration of acetazolamide. The arterial and venous difference in blood ammonia in these patients became significantly smaller after acetazolamide administration. This pointed to an impairment of ammonia uptake by the tissues following acetazolamide administration.

In the present small series it would be impossible to draw any conclusions regarding a difference between the effect of hydrochlorothiazide and chlorothiazide on blood ammonia. It is interesting to postulate that the descending order of carbonic anhydrase inhibition manifested by acetaozlamide, chlorothiazide, and hydrochlorothiazide as mentioned earlier, parallels a descending order of effect on increasing blood ammonia in these three drugs. The present data suggests that hydrochlorothiazide administration is less frequently followed by rises in blood ammonia than is chlorothiazide while the latter is believed not to cause a rise in blood ammonia as consistently as acetazolamide. This suggests the interesting biochemical phenomenon that carbonic anhydrase inhibition may be related in some manner to increases in blood ammonia. Whether this is true and whether there is a real difference in the effect of hydrochlorothiazide on blood ammonia compared to chlorothiazide, only time and further experiment and observation will tell.

Summary

Hydrochlorothiazide is a new oral diuretic which, in most cases, appears to be as effective as chlorothiazide at 1/10th the dosage. Urinary electrolyte excretion patterns with the two drugs vary in that hydrochlorothiazide more consistently produces a greater excretion of chloride ion and less bicarbonate and causes more of a tendency towards alkalosis. It thus resembles more the action of the mercurials and less of the carbonic anhydrase inhibitors than does chlorothiazide. There appears to be a slightly longer duration of activity with hydrochlorothiazide with saluresis continuing significantly at the end of ten hours while with chlorothiazide, excretion falls near base-line levels by the end of ten hours.

The optimal dosage appears to lie between 50 and 100 mg. or .7 to 1.5 mg./kg. No adverse hematological effects have been noted in the present small

series or in a larger series of 39 patients who have received hydrochlorothiazide over the past six months. The only side-effect noted has been epigastric distress in two of these patients.

A decrease in serum potassium following repeated daily administration occurred in most patients. This can be corrected by daily supplementary potassium, approximately 30 to 70 mEq. per day.

On the basis of our limited but quantitative studies on five cirrhotic patients, it would be impossible to draw any conclusions regarding a difference in the effect of either drug on blood ammonia, or the production of hepatic encephalopathy. Both drugs, however, seem safer than acetazolamide in this respect. It would appear that hydrochlorothiazide represents a valuable addition to the constantly improving armamentarium of the oral diuretic agents.

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LYMPHATIC VARICOSITIES OF THE GASTROHEPATIC LIGAMENT

A Report of Three Cases

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Although hepatovenous congestion is known to result in increased prominence of and flow from the liver lymphatics[1], the presence of lymphatic varicosities of the gastrohepatic ligament in the absence of gross liver disease has not previously been described. Accordingly, the operative findings in the following three cases of pancreaticobiliary disease seem worthy of reporting.

Fig. 1

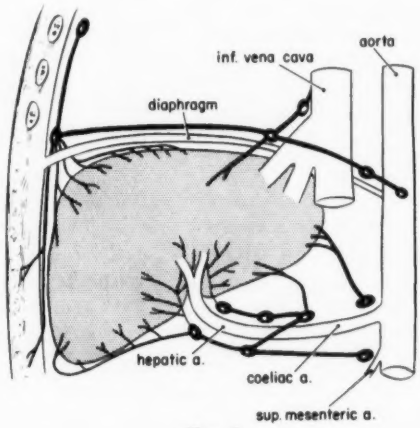

Fig. 2

Fig. 1—Lymphatic varicosities of the gastrohepatic ligament.
Fig. 2—Diagram of the lymphatic drainage of the liver, in sagittal section.

Case Reports

Case 1:—A 48-year old white female had a pancreaticoduodenectomy with choledochojejunostomy and gastrojejunostomy for carcinoma of the ampulla of Vater on 12 February 1955. At operation, a myriad of small lymphatics 1 mm. in diameter enmeshed the common duct; one large lymphatic duct 3 mm. in diameter coursed posterolaterally from the gallbladder. The liver was of normal size and free from metastasis. The lymph nodes of the liver and biliary passages

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were enlarged and friable. Diffuse calcification of the pancreas was noted at surgery. The patient expired 19 February 1955. No autopsy was obtained.

Case 2:—A 26-year old white female had a cholecystectomy for chronic cholecystitis with cholelithiasis 1 August 1956. At operation, the first part of the duodenum and the transverse colon were attached to the inferior surface of the gallbladder with fine fibrous adhesions. No gross disease or enlargement of the liver was noted. Further exposure after peritoneolysis showed that the foramen of Winslow was obliterated by a spongy translucent mass of varicose lymphatics. This lymphatic mass was 6 cm. in diameter. The largest lymphatic vessel contained therein was 3 mm. in diameter. A clear liquid was presumed to be lymph drained from several lymphatic trunks. The hepatic pedicle nodes were enlarged and friable. The postoperative recovery of the patient was uneventful.

Case 3:—A 59-year old white female had a choledochostomy, duodenotomy, and sphincterotomy of the ampulla of Vater on 12 November 1956 for chronic pancreatitis with calculi. Multiple small lymphatics obscured the portal triad.

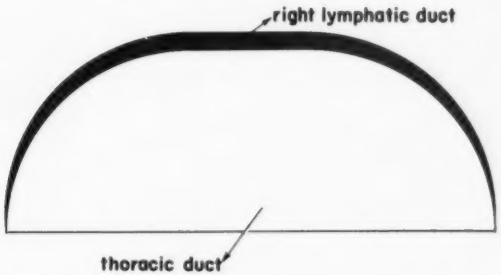

Fig. 3—Lymphatic drainage of the liver, with diagrammatic representation of direction of flow.

The liver was of normal size but showed several small oval areas of gray subserosal pigmentation on its inferior surface. The lymph nodes of the biliary passages and liver were enlarged and friable. Diffuse calcification of the pancreas was noted at surgery. Postoperative recovery was uneventful.

A review of the literature shows that Pribam and Upham[3] have described *Lymphangitis hepatica* or "Lymphatic Hepatitis" as an allergic form of hepatitis, originating within the liver, associated with moderate hepatomegaly, and secondarily involving Glisson's capsule, and the subserosal tissues of the gallbladder and the gastrohepatic ligament. They noted lymphatic obliteration and cicatrization rather than lymphaticomegaly. The *Zuckergussleber*[4] of perihepatitis was explained on this basis. Enlarged friable lymph nodes of the gastrohepatic ligament have previously been reported in biliary cirrhosis.

The lymphatic anatomy of the liver is so arranged that both ascending and descending pathways for lymphatic drainage are present. The anterior superior

surface of the liver sends afferent ascending lymphatic trunks through the diaphragm to anastomose with the anterior pre-pericardiac group of lymphatics. Efferent lymphatic trunks from these nodes travel to the right lymphatic duct or the thoracic duct via the internal mammary nodes. The liver is thus uniquely provided with dual drainage to both the right lymphatic duct and thoracic duct. Additional ascending pathways follow the hepatic veins and the inferior vena cava to empty into the thoracic duct.

The great bulk of the lymphatic drainage of the liver travels through the 15 to 18 descending collecting trunks that accompany branches of the portal vein, hepatic artery, and biliary tree in the gastrohepatic ligament. The lymphatic drainage of the liver is via nodes clustered along the coeliac axis and its

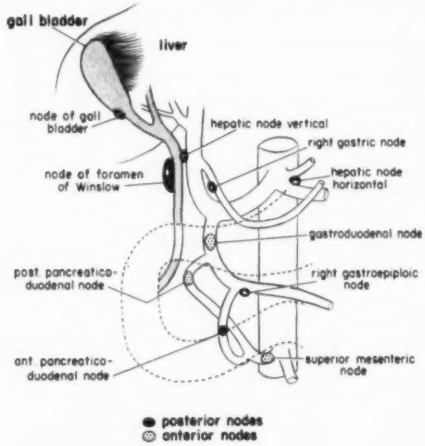

Fig. 4

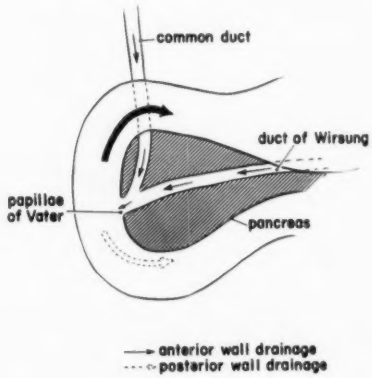

Fig. 5

Fig. 4—Lymphatic drainage of the liver, primary and secondary lymph node echelons.
Fig. 5—Lymphatic anastomoses at the papillae of Vater.

branches: hepatic, gastroduodenal, right gastroepiploic, right gastric and pancreaticoduodenal.

This liver lymph reaches the thoracic duct via the coeliac nodes. Efferent lymphatic trunks from the umbilicus and falciform ligament accompany the hepatic lymphatics in the portal triad. Lymphatic drainage from the gallbladder and biliary ducts traverses sentinel nodes of the gallbladder, foramen of Winslow and ampulla of Vater. These lymphatics travel posterior to the pancreas to empty into the superior mesenteric node. There is an extensive anastomosis between the lymphatics of the liver and biliary passages, primarily within the gastrohepatic ligament.

The gallbladder and biliary passages have a communicating mucous and periductal lymphatic network. Lymph is routed along the nodes of the biliary

passages (node of the gallbladder, node of the foramen of Winslow) to the posterior superior pancreaticoduodenal node in the region of the ampulla of Vater. The periductal lymphatics accompanying the duct of Wirsung flow in the direction of the ampulla of Vater. The mucosal and serosal plexuses of the duodenum anastomose freely but seldom have direct intramural connections with the gastric lymphatics at the pylorus. The anterior duodenal collecting trunks are routed via the horizontal hepatic node in the region of the coeliac axis. The posterior duodenal collecting trunks travel with those of the biliary passages to the superior mesenteric node.

Comment

Three cases of biliary pancreatic obstruction showed the following triad of operative findings:

1. Lymphatic varicosities in the gastrohepatic ligament.
2. Enlarged, friable hepatic and biliary lymph nodes.
3. Normal sized liver.

In our opinion, these were cases of lymphangiectasis rather than lymphangioma. The extensive rerouting of lymph can best be explained on the basis of lymphatic obstruction at or near the ampulla of Vater. The absence of chyle in the involved lymphatics is probably due to the fact that the adjacent organs contributing to the collateral lymphatic circulation do not participate in fat absorption. Difficulty in recognition of the transparent lymphatics of the gastrohepatic liagment would be simplified by use of lipophilic dyes at surgery. In the future, this triad will be a sign to us that extensive pancreatic and biliary exploration is warranted.

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GASTRIC CANCER

RENÉ A. GUTMANN, M.D., F.A.C.G. (Hon.)*

Paris, France

I had the opportunity of reading several papers, congress or panel discussions, which appeared in the North American medical journals. I will not here write an exhaustive study about the matter, but I want to emphasize some facts which seem to me of special importance.

Ulcerating Forms

There is absolutely no means of making a precise diagnosis about the malignant or the benign nature of a niche by its radiological appearance. The size of the niche, which is so often referred to, is absolutely worthless. A benign ulcer may be enormous (giant ulcer) and practically all the numerous cancers in which we could make an early diagnosis were very small, and sometimes nearly invisible.

The irregularities in the outline of a niche may be inflammatory and benign as well as organic and malignant.

The fact that a niche is protruding or included inside the gastric profile has no meaning. I allude especially to the "meniscus complex" which is considered a sure malignant sign. I have seen many benign ulcers with a typical "meniscus".

The irregularity of the surrounding folds may be benign as well as malignant.

The "pad" around the niche, which characterizes itself on the film by a transparent semicircle, may be seen in small ulcers as well as in small cancers.

All these signs may be of interest in statistics, but when one is in the presence of a patient, the question in point is not the knowledge of the percentage of a sign in benign and malignant lesions, it is obviously to make a decision: is this particular patient to be treated or operated on? In this circumstance, none of these signs permits a conclusion.

I have described many suspicious aspects of the niches (*niche en plateau*, etc.), but I will not here belabor this point, because they are only "suspicious", and not pathognomonic.

Having studied this question for over 30 years, I can say that the only means of answering it (at least until this very day) is to make a preliminary treatment. Thirty years ago, I proposed what I called the "therapeutic test". It

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consists in treating the patient for about two months and in comparing the films taken before and after the treatment.

May I say that a treatment of staying in bed, in having a severe diet†, antispasmodics and powders (even through a duodenal tube) is absolutely insufficient for the test. Of course, if in these conditions the niche disappears, it is a proof of benignity; but its persistence has no significance, because a benign niche may resist that which an active treatment could have cured.

We use in France, for the test, injections of active products (intravenous proteinotherapy; I use now intramuscular injections of sodic oxyferriscorbon). It is not possible for me to discuss exhaustively here the treatment of ulcers and the therapeutic test; one may find them in my books.

It may be necessary sometimes to repeat the therapeutic test, followed of course with another x-ray examination.

In dealing with this test, one must always consider the possibility of a benign ulcer having degenerated into a cancer.

There are, from this point of view, two different parts of the stomach.

On the *vertical* part, I have never seen, on the lesser as well as on the greater curvature, the degeneration of a benign ulcer. So here, when the niche diminishes, one can affirm its present and also future benignity.

On the *angulus*, the *horizontal* part and also on the *pylorus*, every benign ulcer may be the seat of a cancer•. So we need, if necessary with renewed treatments to bring about the entire disappearance on the film of all the pathologic signs. Otherwise, it is better to operate.

I have never seen the therapeutic disappearance of a malignant lesion. All the published cases I have read are the result of successive radiographs taken in different and faulty incidences or of wrongly interpreted clinical or radiographical data.

The rule of nondisappearance holds not only for orginally cancerous niches, but also, in all the cases I have observed, for ulcers in a state of cancerous transformation.

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†May I add that, even in the treatment of ulcers (gastric and duodenal), bed, milk diet, and especially treatments and feeding through the duodenal tube, seem to me to be an anachronic torture. All my patients, except in very acute cases, follow a nearly normal diet and lead their normal life. They are allowed to smoke, but only after meals.

•When we consider only ulcers of the angulus, of the horizontal part and of the pylorus, properly treated and not clearly diminishing after the treatment, the percentage of degenerated cases is about 8.

This number does not include those cases which are too advanced to allow us to know whether the initial lesion was benign or malignant.

Of course, if one considers the total ulcers of the stomach, *immediately* operated on, without a preliminary medical treatment, this greater number of cases lowers the percentage. This allows some authors to write that degenerated ulcer is rare.

The clinical and paraclinical facts are to be entirely neglected for the diagnosis.

In the early detected cancers, there is generally no loss of weight, no anemia, no anorexia, no change of gastric acidity, etc. There is of course no tumor, no increasing of glands. For those who are not persuaded of these facts, it is needless to try to make an early diagnosis.

The counterpart of these notions must not be forgotten.

It seems to me, for instance, an error to consider that an ulcer with achlorhydria or hypochlorhydria is surely malignant, those symptoms not being rare in benign gastric ulcers.

It seems to me an error to operate on a patient with anorexia, loss of weight and no radiographical signs on the stomach, supposing that these symptoms are the consequence of a small cancer, not yet radiographically visible. When a gastric cancer is accompanied with such symptoms, it is surely a relatively advanced cancer and a correct x-ray examination must show its presence.

It seems to me an error to consider that all the niches of the greater curvature are malignant and must be operated on. I have seen and medically cured many benign ulcers on this greater curvature. Here also the law of the stomach's two parts holds good: most of the niches are benign on the vertical part, most are malignant on the other parts (see above) and all must be submitted to the therapeutic test.

Another very important consequence of these facts is the following: it is frequent, in a patient bearer of a gastric cancer in its beginning, to observe, after a medical treatment, a clinical improvement and often a clinical healing. *The only important facts are the radiological ones.* The clinical healing joint with the radiological increase of the lesion is even an absolutely certain sign of cancer. So not to have a patient x-rayed after each treatment of a gastric lesion is to play heads and tails with the patient's life.

To sum up, if, of course, one considers it of no importance to remove a stomach which one could have cured medically, it is always correct to operate immediately on all "niches". So one escapes from the difficulty of the diagnosis and from the responsibility. But this is exactly the contrary of what I consider the correct medical way of thinking and of doing. Gastrectomy ought to be done *only* if it *cannot* be avoided.

So having medically and definitively cured the majority of patients with proved benign ulcers, while preserving their stomachs, I can absolutely not agree with the opinion that gastric ulcers *must* be operated on "since the presence of an early cancer cannot always be excluded, short of placing the ulcer under the microscope". I do not consider, in 1959, gastrectomy as a means of diagnosis.

The argument that "operative mortality is very low" could as well be alleged in favor of amputation as a correct treatment of whitlow.

In the diagnosis of gastric cancer in its early stage, one must not fear of "losing time" with the therapeutic test, even repeated, if necessary and if the lesion begins to diminish, two or three times.

Gastric cancer evolves, in its very beginning, not, as it is classic, through the weeks or the months, but *through the years*, four or five years being the ordinary length. The same notion applies as well to the ulcerative form as to the infiltrating one, where the evolution can be even longer*.

It is not the right place to here develop that notion; but I have innumerable observations of this long evolution: cancers radiologically clear and unrecognized during several years and through several x-ray examinations (I presented some of these observations at the World Congress of Gastroenterology last summer in Washington).

When a patient is moved, by some mild troubles, to consult a physician, the diagnosis can be made in the early period, as well in the ulcerating forms as in the infiltrating ones, *if* the patient is sent to be x-rayed, *if* the radiologist knows the signs of early cancer (see hereafter) and *if* the therapeutical test is correctly utilized. Too often, however, this diagnosis, especially in the infiltrating forms, is only made when unmistakable signs are present, at the "classical period", which signifies too late.

Of course, there are cases in which the cancer evolves without troubles and reveals itself tardily with advanced signs. This does not indicate that the real evolution has been as short as it appears. Of course also, it is not possible to make a useful diagnosis when the patient does not consult the physician in time!

In more than 30 years of clinical, radiological and gastroscopical studies, in which I have discovered many early cancers, I have never met one case in which the diagnosis of an incipient cancer has been made by gastroscopy. This is not an attack against gastroscopy, which is a very interesting method and irreplaceable in gastritis for instance. It is only a simple remark concerning the services gastroscopy has rendered to me in the early diagnosis of gastric cancer. In cancer, gastroscopy has very little value†.

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*The longest evolution I have observed is 12 years. Pains, unrecognized cancerous signs, Krukenberg tumor removed; circumstances of war hindering further explorations; increasing of pains; finally, 12 years after the beginning, huge gastric cancer.

But there is not an obligatory relation between the length of the evolution and the degree of the cancer. After 3 years, for instance, a cancer can be still limited to the mucosa or, only in one point, penetrating through the *muscularis mucosae* (I have observed such cases). So, paradoxically, a cancer evolving since 3 years can be "in its beginning", anatomically speaking.

†I must say these opinions are strictly objective. I am myself neither a radiologist nor a gastroscopist.

Cytology is also a very interesting method for statistics. It is indeed exciting to compare its results with those of the operation. But our work is not to establish statistics; it is to make as early and as useful a diagnosis as possible. In cytology, the incidence of "false positive" and "false negative" results impairs the trust in it, when one has, in the presence of a patient, to decide for or against an operation.

Infiltrating Forms

In panel discussions, it seems to me that one has not given these forms their real importance.

Here the problem is no more, like in the ulcerous-like forms, to decide whether a niche is benign or malignant. It is not to let the radiological signs *escape* and the cancer remain unrecognized. This happens with incredible frequency. So, in the long evolving cancers, there are more infiltrating forms than ulcerating ones.

It is not my aim to describe thoroughly here the radiological signs of this variety of cancer.

I shall only say briefly that it reveals itself by a localized stiffness, but this stiffness can remain unrecognized for different reasons, other than that it may be very small in extent. For instance, it may be, in the same time, "stiff and flexible" (like a corset steel) and it can change its orientation on successive films according to the peristaltic contractions (like driftwood on the waves) and also according to the vertical or horizontal position of the patient.

It can be beneath the gastric profile (all the varieties of "embedded appearance"). It can touch the angulus, transforming it in a rigid line and giving to this angle a stiff and widened appearance.

The too frequent nonrecognition of these details, and of many others, leads to a serious and often fatal consequence.

Tumoral Forms

Those forms are very rarely the object of an early diagnosis. The reason is that the cancer does not usually begin with a growth as it is a rule for the growth to develop itself secondarily and lately upon an ulcerating or infiltrating lesion.

The only exception is the cancerous degeneration of a benign tumor.

Such are some of the thoughts I want to express. May I add some general remarks.

One often sees the expression "cancer *in situ*" used to designate a cancer limited to the mucosa. It should be remembered that the "cancer *in situ*" is a

lesion with cytological monstrosities, but without architectural disturbances of the mucosa. So it can be—by those who consider anarchy as the indispensable signature of malignancy—denied to be a real cancer, though, for the majority of authors (and for myself), its precocious cancerous nature is certain.

The cancer limited to the mucosa, with both cytological and architectural disturbances, is the "Cancer No. 1" of the international nomenclature, of which we have, my collaborators and myself, diagnosed, operated and verified about 400 cases*.

I have read that "we have lamentably little information" concerning this kind of lesion.

May I remind you that all these lesions are thoroughly described at the clinical and radiological points of view in my first book about gastric cancer (*"Le cancer de l'estomac au début"*, Paris, 1939, Doin edit.). The histological part, written by I. Bertrand, occupies 140 pages with 127 reproductions of histological slides and operative pieces. It is the first complete histological study of *cancer incipiens* of the stomach.

In my last book (*"Le diagnostic du cancer de l'estomac à la periode utile"*, Paris, 1956, Doin edit.), one can find many details about radiology, clinic and evolution, and also several pages about histology (though, not being an anatomopathologist, I have not developed this part).

And I have even taken the trouble, for my American friends, to translate the major part into English.

This article deals only with incipient cancer and with very small cancers. In the advanced cases, with their conjunction of classical symptoms and signs, there are generally no difficulties in the diagnosis (except for the supracardial forms and for certain extended gastritis) and the surgical indications are clear.

When an early diagnosis is made, one can hope that the patient is definitely cured.

*One may be surprised to see a cancer limited to the mucosa asserting itself by stiffness or by a small niche. Guy Albot's researches have proved that these mucosal cancerous lesions are accompanied with a reactionary noncancerous hypertrophy of the submucosa, which is the basis of the radiographical signs.

NEWS NOTES

Sixth International Congress of Internal Medicine

The Sixth International Congress of Internal Medicine will be held in Basle, Switzerland, 24-27 August 1960. The meeting has been organized under the sponsorship of the International Society of Internal Medicine, Sir Russell Brain, F.A.C.P. (Hon.) of London, President. The President of the Congress is Prof. Dr. A. Gigon and the Secretary is Prof. Dr. H. Ludwig, both of Basle.

The principal subjects to be covered by the Congress will be: Pathogenesis and Therapy in the Edema; Enzymic Regulations in the Clinic. There will be panels on Interstitial Nephritis, Nephrosis, Diuretics, Diagnostic Values of Enzymes and Serology in Rheumatic Diseases.

Programs and registration forms for the Congress may be obtained from the Secretary, Steinentorstrasse 13, Basle 10, Switzerland.

"Voice of Medicine"

Excerpta Medica Foundation announces the publication of a recorded medical journal to be published under the title "Voice of Medicine". Recordings of discussions and interviews taken during national and international medical congresses, clinical pathological conferences, world health assemblies, medical meetings and symposia will be published. There will also be included discussions by leading specialists on subjects of current medical interest arranged by Excerpta Medica on an international level.

Further information may be obtained from the Excerpta Medica Foundation, 2 East 103rd Street, New York 29, N. Y.

In Memoriam

We record with profound sorrow the passing of Dr. Victor Willner, New York, N. Y., Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

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ESOPHAGUS

NEUROMUSCULAR DISORDERS OF THE ESOPHAGUS: Frederick S. Cross. Clin. Med. 5:1499 (Nov.), 1958.

By the use of cinefluorography, and intraluminal pressure studies of the esophagus, two basic types of neuromuscular imbalance of the esophagus have been defined.

The type called "neuromuscular failure" is characterized by delay in transit of barium from the thoracic to the lower esophagus with the patient in the supine position. Misswallowing with aspiration into the trachea, and regurgitation are common. Intraesophageal studies indicate hypotonicity and hypoactivity of the entire esophagus. This type usually occurs in older people, and is frequently found and associated with hiatus hernia, and achalasia.

The type called "segmentation" has also been labelled pseudodiverticulosis and tertiary peristalsis. It is characterized by alternating areas of narrowing and pseudodiverticulum formation in the lower esophagus. Pressure studies indicate that the upper one-third of the esophagus is normal or hypotonic, whereas the lower two-thirds is hypertonic and hyperactive. This results in a functional obstruction between the upper one-third and the lower two-thirds of the esophagus. Segmentation is frequently found unassociated with organic disorders.

Both forms of neuromuscular disease may be discovered by careful fluoroscopy, though photofluorography and intraesophageal pressure studies are valuable adjuncts in studying the neuromuscular mechanism in detail.

WALTER LENTINO

THE TREATMENT OF ACHALASIA OF THE ESOPHAGUS (CARDIOSPASM): Lamar Soutter. Am. Pract. & Digest. Treat. 9:1796 (Nov.), 1958.

The essential fault in achalasia of the esophagus is a diminution or complete loss of the peristaltic wave which normally propels food downward, the resulting lack of reflex opening of the lower segment of the esophagus, and a loss of peristaltic motion through this segment into the stomach. To the surgeon the terminal esophagus commonly displays a hypertrophy of the circumferential fibers, fibers which normally are hard to find. Less commonly this region is soft, atonic but grossly indistinguishable from a normal esophagus. Care must be taken in establishing a diagnosis before

treatment is undertaken. A good history, fluoroscopy and x-ray are necessary. Esophagoscopy is only necessary to rule out peptic esophagitis structure, carcinoma or scleroderma when suggested by history or x-ray. Psychotherapy may help the patient tolerate his disorder. Medical treatment is generally ineffective.

Of the methods used for dilating the lower segment, rupture of the circumferential fibers of the lower esophageal sphincter by a pneumatic bag should be tried first and will usually be effective. The author used the Mosher pneumatic esophageal bag dilator with a mercury filled rubber tip and describes the method. He states that it should be carried out only in a hospital well equipped to handle thoracic surgery in the event of rupture of the esophagus which occasionally may occur. Fluoroscopic and x-ray examination are used to determine the positioning and effective dilatation. If the method is not successful a modified Heller myotomy will produce good results. Good results were obtained by pneumatic bag in 8 patients and fair results in 2. The author cites the more extensive experience of Olsen et al as evidence for the effectiveness of hydrostatic dilatation.

ERNEST LEHMAN

STOMACH

THE CLINICAL MANIFESTATIONS OF GASTROILEAL ANASTOMOSIS: A.M.A. Arch. Int. Med. 102:722 (Nov.), 1958.

Gastroileal anastomosis produces lienteric diarrhea with progressive weight loss, weakness, and electrolyte deviation especially potassium deficiency. This symptomatology starts one to two weeks after an operation for peptic ulcer. Belching of malodorous gases and fecal vomiting are also characteristic symptoms. X-ray examination has not been diagnostic in the majority of the cases. However, refilling of the stomach with barium after it had previously emptied is typical of this disorder. Differential diagnosis must consider mainly gastrojejunocolic fistula which occurs rarely in women, which follows almost always posterior gastroenterostomy without resection and does not become symptomatic until a period of one to four months after operation. Symptoms are similar to gastroiliac fistula but are usually preceded by a period of severe ulcer pains.

H. B. EISENSTADT

DUPLICATION OF THE STOMACH: Major Richard E. Green. Am. J. Surg. 96:721 (Nov.), 1958.

Duplications of the stomach are congenital in nature and have the common anatomic characteristics of a wall containing all the normal layers of the stomach, except in the area where they are attached to the stomach proper. This is an unusual and rather rare lesion. The blood supply to the normal alimentary tract and to the duplication is usually the same. An interesting and feasible theory of Bremer is suggested as the plausible cause. This theory recognized that in the six-week old embryo, the intestinal lumen is occluded by rapid proliferation of epithelium. Thereafter, vacuoles develop, and in the usual trend of events, the vacuoles coalesce to form a lumen again. It is postulated that one or more of these vacuoles separate from the lumen of the main channel and may lead to duplication. The treatment is surgical as soon as the diagnosis is estimated.

Only 28 cases of gastric duplication have been reported in the English literature. A case report of a 2-year old white female infant is presented. The diagnosis was made after a long period of observation and after ingestion of food, when it was noted that an abdominal mass appeared which had not been seen several hours before feeding. Operation was performed. The accessory mass was removed and the patient made an uneventful recovery. On microscopic examination, the wall of the cystic mass was lined with well defined gastric mucosa, with hypertrophy. The stomach wall was essentially normal in other respects.

CARL J. DEPRIZIO

CARCINOMA OF THE STOMACH: P. H. T. Thorlakson. Canad. M. A. J. (15 Nov.), 1958.

Early carcinoma of the stomach has no positive physical signs. Early x-ray signs—deformity of gastric contour: loss of normal rugal markings, filling defects, localized rigidity, absent peristalsis, delayed emptying. Ulcer in prepyloric region: ulcer along greater curvature should cause concern. If *any* suspicion, even slightest exists—repeat examination in one month.

Other means of examination must on occasion be brought in—gastric analysis, stool examination for occult blood: cytological examination of gastric washings: gastroscopy: exploratory laparotomy.

The author then discusses his statistics of gastric ulcer—cancer problem ten per cent of reported radiological benign ulcers are found to be malignant. The author's clinic operates on 60 per cent of all cases with a diagnosis of chronic gastric ulcer. A gastric ulcer which has not healed in 6 weeks by x-rays, should be treated surgically. The author then discusses the various technics of gastric resection for carcinoma of stomach.

All in all, gastric malignancy awaits a method of earlier diagnosis—when lesion is in quiet stage. A plea is made to pay particular attention in the very early almost insignificant symptoms in patients over 40 years of age.

LIONEL MARKS

PRIMARY GASTRIC LYMPHOSARCOMA WITH TEN YEARS' SURVIVAL: Kent W. Barber and Robert W. Taylor. Illinois M. J. 114:230 (Nov.), 1958.

Two cases are presented with large, smooth masses occupying midportion of the stomachs, both cases going to surgery with diagnosis of carcinoma.

Laparotomy with gastrostomy revealed large, smooth masses filling most of the lumen of the stomachs.

In one case a subtotal resection of three-fourths of the viscus was performed; in the other total gastrectomy was done with esophagoduodenostomy anastomosis.

Examination of adjacent lymph glands, in both cases, showed no metastatic involvement, and in view of this no radiotherapy was instituted.

Follow-up of both patients indicated fairly comfortable living with need for occasional treatment of hypochromic anemia, resulting probably, from the radical dissection.

X-ray studies showed normally functioning anastomoses, with no recurrence of malignancy, since operation in 1948.

J. EDWARD BROWN

COMBINED GASTRIC AND DUODENAL ULCERATION: R. Mangold. Brit. M. J. 5106:1193 (15 Nov.), 1958.

The authors give a statistical study of 157 cases of combined gastric and duodenal ulcers, including only cases of gastric ulcer at or above the angulus. The incidence was about three per cent of the total number of ulcers studied. The classical explanation of duodenal obstruction with gastric retention leading to combined ulcers was negated. In less than 30 per cent were any possible signs of pyloric stenosis found. There is a suggestion of a common hereditary background in similar cases reported in the literature. It was felt that the factor causing either the gastric or duodenal ulcer disease was at work to cause combined ulcers. Attention is called to the higher risk of bleeding in combined ulcers.

BERNARD FARFEL

CONGENITAL ATRESIA OF THE DUODENUM: G. I. W. Cottam and W. A. Arneson. J. Lancet 78:465 (Nov.), 1958.

The authors report a case of congenital atresia of the duodenum in a newborn male operated in 1937. A gastrojejunostomy was done. The patient had seven other congenital anomalies, none of which were disabling. The patient did well for 11 years, and development was normal. In December, 1948, he developed epigastric distress associated with anemia due to bleeding internally. After four episodes of melena in

six years, surgical exploration revealed bleeding from the stoma and an ectopic piece of pancreas in the anterior gastric wall. It was then discovered that the atresia was caused by annular pancreatic tissue and scar. The old gastrojejunostomy was disconnected, the ectopic pancreatic tumor was excised, and a duodenoduodenostomy was done. The patient is now a perfectly well 21-year old male, four and one-half years after the secondary operation.

SAMUEL M. GILBERT

SOME OF THE NEWER THEORIES OF THE ETIOLOGY OF PEPTIC ULCER: John Tilden Howard. Texas J. Med. 54:764 (Nov.), 1958.

This article is an interesting resumé of all the various theories of the etiology of peptic ulcer.

The author's theory is that there is some factor as yet unknown which lowers the ability of the mucosa to resist the digestive juices and acids and that the hope for the future in peptic ulcer is that the exact mechanism of the destruction of this resistance will be discovered and means to increase this resistance will undoubtedly follow.

PAUL LEDBETTER

INTESTINES

ADENOMATOUS POLYPS OF THE COLON AND RECTUM: Harry W. Schoenberg, William T. Fitts, Jr. and Horatio T. Enterline. Geriatrics (Nov.), 1958.

Cancer of the colon and rectum is on the increase. It is rapidly becoming the most common site of cancer of the gastrointestinal tract. It behooves all of us to be on the lookout for this type of a tumor and reduce its onslaught. To do this, we must spot the premalignant lesion; namely the adenomatous polyp.

Evidence exists that cancer of the rectum arises from polyps; early detection of polyps should be part of the routine examination of every patient over 40. The majority of polyps are in the distal 25 cm. of the large bowel; this is within reach of the sigmoidoscope.

Adenomatous polyps are frequently multiple. Thirty-three per cent have more than one polyp, 18 per cent more than two polyps. When polyps are removed 40 per cent of patients develop subsequent polyps. Bleeding per rectum is present in over 50 per cent of cases. The author goes into detail as to treatment of these polyps. This includes the sigmoidoscopic and the operative approach.

When local removal of polyps are done, a 6-month follow-up study for life is advocated.

LIONEL MARKS

UMBILICAL HERNIA: Preston J. Burnham. Am. Pract. & Digest. Treat. 9:1785 (Nov.), 1958.

A simple technic for repair of umbilical hernia through a small curved transverse incision with preservation of the umbilicus is described as a substitute for the present mutilating type of operation. The method is offered because it gives an excellent cosmetic result and produces no tension on the *linea alba*. The author has employed the method in 7 patients aged 6-62 years.

ERNEST LEHMAN

SALMONELLOSIS AND ALLIED BACTERIAL DIARRHEAL DISEASE: Gordon McHardy and Robert J. McHardy. Am. Pract. & Digest. Treat. 9:1803 (Nov.), 1958.

A practical review and classification of the subject of bacterial diarrheal disease is presented. A more aggressive clinical approach toward definitive bacteriologic diagnosis and more specific chemotherapy is urged. Outbreaks render epidemiologic studies imperative. In order of frequency the diarrheal etiologic agents are: salmon-

ella, shigella, staphylococcus, E. coli, and streptococcus. Afebrile and febrile diarrheal illnesses are caused by different viral agents also. The ECHO viruses may be responsible for a "steatorrheal enteritis" in man. Differential diagnostic procedures include: history of contacts; physical examination including proctosigmoidoscopy; gross and microscopic stool examination; parasitologic survey and bacteriologic identification. The clinical characteristics are described. Salmonellosis is most commonly due to food or drink contaminated with *S. typhimurium*. Supportive measures and a short intensive course of chloramphenicol are used in treatment. Protracted therapy is discouraged. Purgation and sulfonamides may be of value in the simple intoxications and the chronic infections. *Shigella sonnei* or *Shigella paradysenteriae* is responsible for 90 per cent of shigella infections in this country. Rectal swabbings supply material for diagnosis. Sulfadiazine and sulfathiozole are relatively specific, but the tetracyclines, polymyxin, and chloramphenicol have also been declared effective. In staphylococcus enterotoxin and pseudomembranous colitis erythromycin is advocated. Enteritis associated with streptococcus is a debatable etiologic probability. Escherichia, the coliforms and the Klebsiella aerobacter group are involved primarily in infantile diarrheas and occasionally in elderly and severely debilitated persons in institutions. Neomycin and sulfathalidine should be tried prophylactically and therapeutically in institutions. Parasitic induced diarrheas must be considered in differential diagnosis. *Giardia lamblia* is pathogenic and responds to atabrine. Trichuriasis and strongyloides respond to dithiazanine, enterobiasis to dithiazanine or piperazine. Piperazine is curative for ascariasis.

ERNEST LEHMAN

ABDOMINAL AORTOGRAPHY (CONCLUDED): Owings W. Kincaid and George D. Davis. New England J. Med. 259:1067 (27 Nov.), 1958.

This article concerns itself primarily with renal arteriography. The arteriography may be performed by injecting the dye through a needle which has been placed in the aorta above the renal arteries or else in a retrograde manner through the femoral artery. A normal nephrogram implies considerable integrity of the intrarenal circulation and renal tubular function. The procedure is very useful in detecting anatomic changes in the kidney such as congenital and hydronephrosis. Vascular lesions such as arterial occlusion and aneurysms may also be diagnosed. The differentiation between renal tumors and cysts are also discussed as is the usefulness of arteriography in certain gynecological conditions.

The incidence of complications is 1.02 per cent and ⅓ of these are due to renal damage which is clinically manifested by renal insufficiency. Neurologic complications which consist of muscle paralysis are second in frequency to renal damage and may be permanent. Injection of the medium into a mesenteric or celiac artery is rare but has been reported. Fortunately serious hemorrhage is also very rare.

The contraindications to aortography are renal damage and those for any surgical procedure requiring anesthesia.

THEODORE COHEN

INTUSSUSCEPTION IN INFANCY AND CHILDHOOD: Mark M. Ravitch. New England J. Med. 259:1058 (27 Nov.), 1958.

The author discusses a series of 47 cases of intussusception. The typical history and sites of location are reviewed. Reduction in most cases was successfully accomplished by barium enema, the technic of which is discussed. The position of the apex of the intussusception and the duration of symptoms have little to do with the likelihood of successful reduction. A flow of barium into the ileum is regarded as mandatory for being certain that reduction has been accomplished. Following this the patients were given powdered charcoal by mouth and six hours later an enema was performed. The recovery of charcoal in the enema returns proved beyond doubt the success of the therapy. Reduction of gangrenous bowel or perforation did not occur. Those cases which did not respond medically were operated on.

THEODORE COHEN

CHRONIC CONSTIPATION: Marvin Gasster. Med. Times 86:1403 (Nov.), 1958.

Emotional factors, training patterns, diet, work habits, and antacid or adsorbent medication have brought about a sharp increase in the use of anticholinergic and ganglionic blocking drugs, which have powerful constipating effects. Each patient who is constipated presents an individual problem, usually complicated by the use of cathartics of one kind or another.

Bile preparations are considered to be mild, physiologic stimulants to evacuation and, in addition, they enhance the effectiveness of other stimulant cathartics.

In this paper veracolate was the preparation used in the successful treatment of 104 patients.

I. HENRY EINSEL

RADICAL SMALL BOWEL RESECTION: REPORT OF TWO CASES: Paul H. Jordan, Jr., John R. Stuart and John D. Briggs. Am. J. Digest. Dis. 3:823-843 (Nov.), 1958.

In addition to reporting two cases of their own, the authors reviewed 44 cases reported in the literature concerning radical small-bowel resection defined as removal of 75 per cent or more of the mesenteric small bowel. Evaluation of the postoperative results indicated that 77 per cent of patients with resections of this magnitude were not invalid. Although the study of these cases did not conclusively indicate the relative importance of the jejunum and ileum for maintenance of nutrition, the results appeared best when a portion of the ileum rather than a segment of jejunum remained. Satisfactory results following resections in this category depend in part upon the patient's psychological motivation and on continuous careful management of his diet and health, particularly during periods of stress.

WALTER CANE

THE PROBLEM OF SUSPECTED RECURRENCES IN CANCER OF THE ALIMENTARY TRACT: K. Cronin and H. Ellis. Brit. M. J. 5108:1319 (29 Nov.), 1958.

The article is primarily a series of case reports of recurrent cancer of the alimentary tract treated by secondary resections with an increase in clinical recovery rates.

The authors had, between the years of 1953 and 1957, 31 patients who had laparotomies for suspected recurrent cancer. In 11 of the 31, it was possible to remove the recurrence. The results in these 11 were reasonably good considering the nature of the disease, 4 of the 11 being alive and well from 4 to 17 months following the last excision. Deaths occurred in the other 7 with survival following surgery from 4 to 26 months except for two who died in immediate postoperative period.

The authors conclude that with the possibility of doing right hepatic lobectomy as well as the comparatively simple resection of the left hepatic lobe, re-exploration of the abdomen is now a more feasible treatment for recurrent carcinoma than heretofore thought and that a more optimistic attitude toward the surgical treatment of recurrent cancer of the alimentary tract is advocated and encouraged.

PAUL LEDBETTER

MULTIPLE HEMANGIOMAS OF THE JEJUNUM AS A CAUSE OF MASSIVE GASTROINTESTINAL BLEEDING: Albert L. Evans, Olin S. Cofer and Hugh H. Gregory. J. M. A. Georgia 47:600 (Dec.), 1958.

Hemangioma of the small bowel is a rare condition which manifests itself by bleeding. Hemangiomas may be associated with or mistaken for intussusception, obstruction or inflammatory intestinal conditions. An absolute diagnosis of hemangioma of the small bowel can only be made by surgery or autopsy. The authors discuss vascular tumors of the small bowel and add a case multiple cavernous hemangioma of the jejunum.

A. J. BRENNER

RATIONAL BASIS FOR MEDICAL AND SURGICAL TREATMENT OF SEVERE ULCERATIVE COLITIS: Juan Nasio. Am. J. Proct. 9:478 (Dec.), 1958.

In spite of the unknown pathogeny of ulcerative colitis, the author points out 12 principles upon which rational treatment of this disease should be based: 1. Paramount importance of psychical treatment; 2. treatment of neurovegetative dystonia; 3. Treatment of infection with sulfonamides and antibiotics with alternative administration of several kinds of the latter; 4. transfusions of total blood is the only therapeutic measure to restore the loss of blood; 5. diet should be agreeable to taste; 6. rehydration must be correlated to the affected extracellular sector; 7. vitamin therapy should not be a supplement to the diet, but of antiinflammatory and healing character. Vitamins C and D_2 in large doses are indicated for the purpose; 8. medical ileostomy or "drip by drip treatment" is excellent to control ulcerative lesions; 9. ACTH and cortisone should be indicated without fear of side-effects; 10. treatment of concomitant diseases and complications is very important to a favorable evolution; 11. surgical treatment depends on prognosis; 12. surgical treatment should not be an effect of fear of malignant degeneration.

Based upon these principles, the author classifies medical treatment of ulcerative colitis in general, and local measures. Among the general measures esteroids, antiallergic (tuberculostatics, azulens), sulfonamides, antibiotics like chlorotetracycline and chloramphenicol succinate salts of gold, chlorchyne, estrogens, somatotrophin, enterogastrone and Vitamins D_2, and B_{12} are valuable; their efficacy depends on each patient, therapeutic combination and intensity and opportunity of the management.

Surgical treatment is required not only in the presence of complications but also in special stages with bad prognosis. Technic of choice is a partial colectomy and simultaneous ileostomy with a minimal mortality rate.

PAUL B. VAN DYKE

LIVER AND BILIARY TRACT

CONSTITUTIONAL HYPERBILIRUBINEMIA (GILBERT'S DISEASE): CASE REPORT AND REVIEW: Alton I. Sutnick and Richard W. Dyke. J. Indiana State M. A. p. 1544 (Nov.), 1958.

The importance of establishing a proper diagnosis of constitutional hyperbilirubinemia is emphasized in order to avoid making a serious prognosis and causing unnecessary surgery. These patients give no evidence of hemolysis, biliary obstruction or hepatocellular damage as a basis for their jaundice. The only evidence of abnormal function is found in the bilirubin excretion test. Of the patients 80 per cent are males with age of onset in early youth or early adulthood. The icterus may be chronic or intermittent and is usually exaggerated by nonspecific stresses. A familial incidence can occasionally be demonstrated. Symptoms during acute episodes consist of lassitude, fatigue, anorexia, nausea and a feeling of fullness in the epigastrium with occasional vomiting. The serum bilirubin is elevated usually, not over 5 mg. per cent, primarily in the indirect fraction. Cholecystography shows good dye concentration and liver biopsy reveals normal hepatic structures. The condition is benign in nature in contrast to the serious nature generally associated with other types of jaundice.

There was another group of patients with essential hyperbilirubinemia, in whom coarse brown pigment is demonstrated in the parenchymal cells of the liver. This "lipochrome hepatosis" was reported by Dubin and Johnson in 1954. These patients are similar in appearance to those with Gilbert's disease, but they have more disturbed hepatic function. They often demonstrate abnormalities in excretory function tests of liver function, abnormal cephalin flocculation and thymol turbidity, frequent bilirubinuria, elevation in serum bilirubin, primarily in the direct fraction rather than in the indirect and nonvisualization of the gallbladder as a rule as contrasted to adequate visualization in patients with Gilbert's disease. Prognosis is uniformly excellent in both syndromes, with the exception of a few infants with Gilbert's disease

who have developed kernicterus.

Schmid recently has shown that the liver forms direct reacting bilirubin by conjugating bilirubin with glucuronic acid. Dubin has suggested that Gilbert's disease may be a defect in conjugation, while the Dubin-Johnson syndrome indicates an inability to excrete the properly conjugated bilirubin glucuronide.

JOSEPH E. WALTHER

HEPATITIS AND CIRRHOSIS IN WOMEN WITH POSITIVE CLOT TESTS FOR LUPUS ERYTHEMATOSUS: Lloyd G. Bartholomew, Albert B. Hagedorn, James C. Cain and Archie H. Baggenstoss. New England J. Med. 259:947 (13 Nov.), 1958.

The author describes a series of 7 cases, mostly in women, who had prolonged jaundice with grave impairment of the liver and hypergammaglobulinemia, the *lupus erythematosus* cell and clinical evidence of *lupus erythematosus*.

The author then describes the 7 cases, giving in detail the history, physical findings, clinical and laboratory data, etc. In the clinical history all showed involvement of multiple systems, with enlargement of the liver occurring late in the illness. All were young women less than 25. All showed migratory joint manifestations, some requiring steroid therapy. Fever was recurrent and unexplained. Urinalysis showed albuminurea, hematurea and cylindrurea. Sensitivity to light was present in 5 of the 7 cases. Urticarial rash was noted in 3 cases. All 7 had anemia with petechea and purpura.

The serum bilirubin was high, 216 mg. direct, 8 mg. indirect. Thymol turbidity and cephalin-cholesterol flocculation were very positive.

Marked hypergammaglobulinemea. Alkaline phosphatase, normal to increased. Concentration of plasma, normal to increased. Sedimentation rate was high. Wassermann was positive. Typical *L.E.* cells were found in serum and bone-marrow.

Liver biopsy done in 3 cases showed that of an acute or subacute viral hepatitis and in 2 cases postnecrotic cirrhosis.

LOUIS K. MORGANSTEIN

JAUNDICE ASSOCIATED WITH ADMINISTRATION OF IPRONIAZID: B. Benaim and M. F. Dixon. Brit. M. J. 5104:1068 (1 Nov.), 1958.

The authors report two cases of jaundice occurring during a clinical trial of iproniazid on 60 depressed patients. Case 1 had received the drug for 72 days to a total of 8.6 gm. when jaundice developed. The course of the disease was unlike that of infectious hepatitis. Case 2 had received the drug for 75 days to a total of 11.25 gm. However, in this instance, it had been combined with Chlorpromazine which has also been reported to cause jaundice. From the evidence available the authors feel that iproniazid may have a direct toxic effect on the liver. Jaundice has occurred in patients receiving as little as 25 mg. daily and it appears unrelated to the duration of the administration; suggesting that an element of idiosyncrasy may be present.

JOHN M. MCMAHON

THE TREATMENT OF CIRRHOTIC ASCITES BY COMBINED HEPATIC AND PORTAL DECOMPRESSION: William V. McDermott, Jr.. New England J. Med. 259:897 (6 Nov.), 1958.

This article is the report of an attempt to relieve portal hypertension and ascites of cirrhosis by combining portal and hepatic decompression.

The case reported is that of a 43-year old man with cirrhosis and ascites who, despite abstinence from alcohol, satisfactory diet and diuretics, had a persistent ascites. After proper hospitalization and laboratory examinations, the patient was explored through a right lateral subcostal and flank incision. The findings were cirrhosis of the liver and portal hypertension. At this operation, the portal vein was severed and a double end-to-side portacaval shunt was constructed. The patient responded to the operation satisfactorily and has done well with a satisfactory diet, the protein restriction of less than 70 gm. daily which prevents a mild ammonia intoxica-

tion, which occurred on a diet of more than 70 gm. protein. The ascites has been completely controlled and there has been a reversal of the hyperaldosteronism.

Since this paper was submitted for publication, the same authors have had five additional patients with intractable cirrhotic ascites. The results have been excellent in all.

PAUL LEDBETTER

BLEEDING ESOPHAGEAL VARICES WITH POLYCYSTIC LIVER: Gilbert S. Campbell, Heinz D. Bick, Elsa Proehl Paulsen, Paul H. Lober, C. J. Watson and Richard L. Varco. New England J. Med. 259:904 (6 Nov.), 1958.

This is a report of three case histories occurring in siblings with polycystic liver and polycystic kidney disease.

The first two cases were in identical twin girls, aged 14, who had been in good health until the onset of massive hemorrhage from esophageal varices. Both of these children had surgery, at which time a splenectomy and splenorenal shunt were done. Later on, both of these children had to have portacaval shunts done, at which time biopsies of the liver and kidneys were done which bore out the diagnosis of polycystic liver disease.

Approximately a year and a half later, the 25-year old brother of these two cases was admitted to another hospital because of severe gastrointestinal bleeding. This patient had a splenorenal shunt with splenectomy and liver biopsy. Nine days following this, a severe hemorrhage occurred and a total gastrectomy was performed. Subsequently, he developed frequent abscesses on the left and throughout his long hospital stay continued to develop multiple abscesses and after further abdominal surgery, expired approximately one year from his original hemorrhage.

This case was autopsied and the article has microphotographs of the liver and kidney sections and biopsies of the other two cases.

PAUL LEDBETTER

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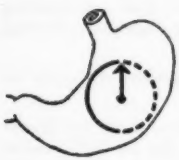

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BOOK REVIEW FOR GASTROENTEROLOGISTS

AMINO ACIDS AND PEPTIDES WITH ANTIMETABOLIC ACTIVITY: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Cecilia M. O'Connor, B.Sc.—Editors for the Ciba Foundation. 286 pages, 28 illustrations. Little, Brown & Co., Boston, Mass., 1958. Price $8.75

In this volume, the reader will find many useful and new prepared chemotherapeutic measures to combat various tumors. Twenty-nine scientists from various countries presented papers expressing their views which may be of interest to the many chemists, biochemists and pathologists who could not be invited to attend because of strict limitation of the number attending.

Very interesting reading may be found on page 38, dealing with amino acid deficiencies on experimental cancer chemotherapy originating from the American Cancer Society and the National Institutes of Health. On page 62, diazoamino acids, etc., are discussed, especially the effect on azaserine by mouse and rat tissue. From the Institute of Experimental Pathology and Therapy of Cancer, U.S.S.R. Moscow, the effeect of chlorethylamine groups on chronic leukemia (myeloid, lymphoid), Hodgkin's and solid tumors, are shown. Illustrative cases are found on page 114. From the Rockefeller Institute for Medical Research, New York, N. Y., a report was given on a group of polypeptide antibiotics which were discovered in the leg wound of a little girl.

For all those interested in the newer aspects of chemotherapy, the book is highly recommended.

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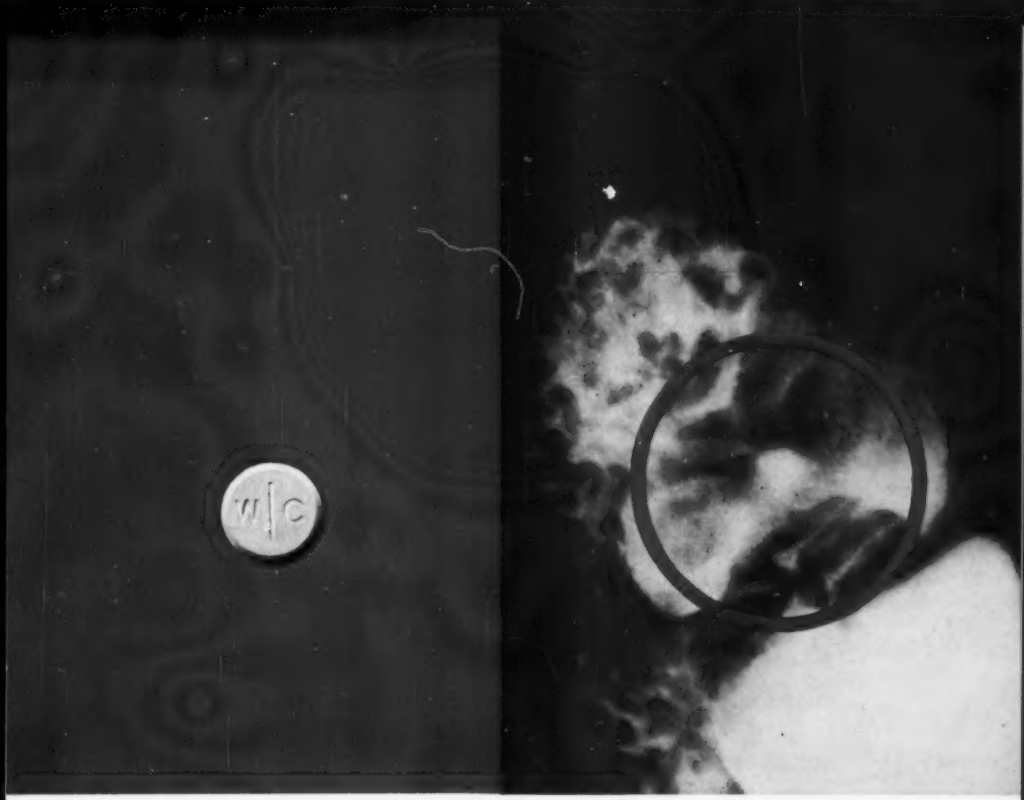
1. *British Medical Journal* 2:827, 1955
2. *American Journal of Gastroenterology* 28:439, 1957



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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V:5 (May, 1958).
2. McHardy, G. et al; Exhibit, So. Med. Assn., New Orleans, La., Nov. 1959.

*Full-color photographs with explanatory text of recent photogastroscopy have been mailed to you.

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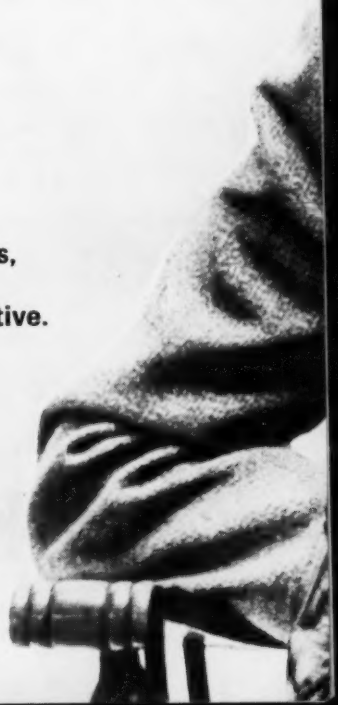

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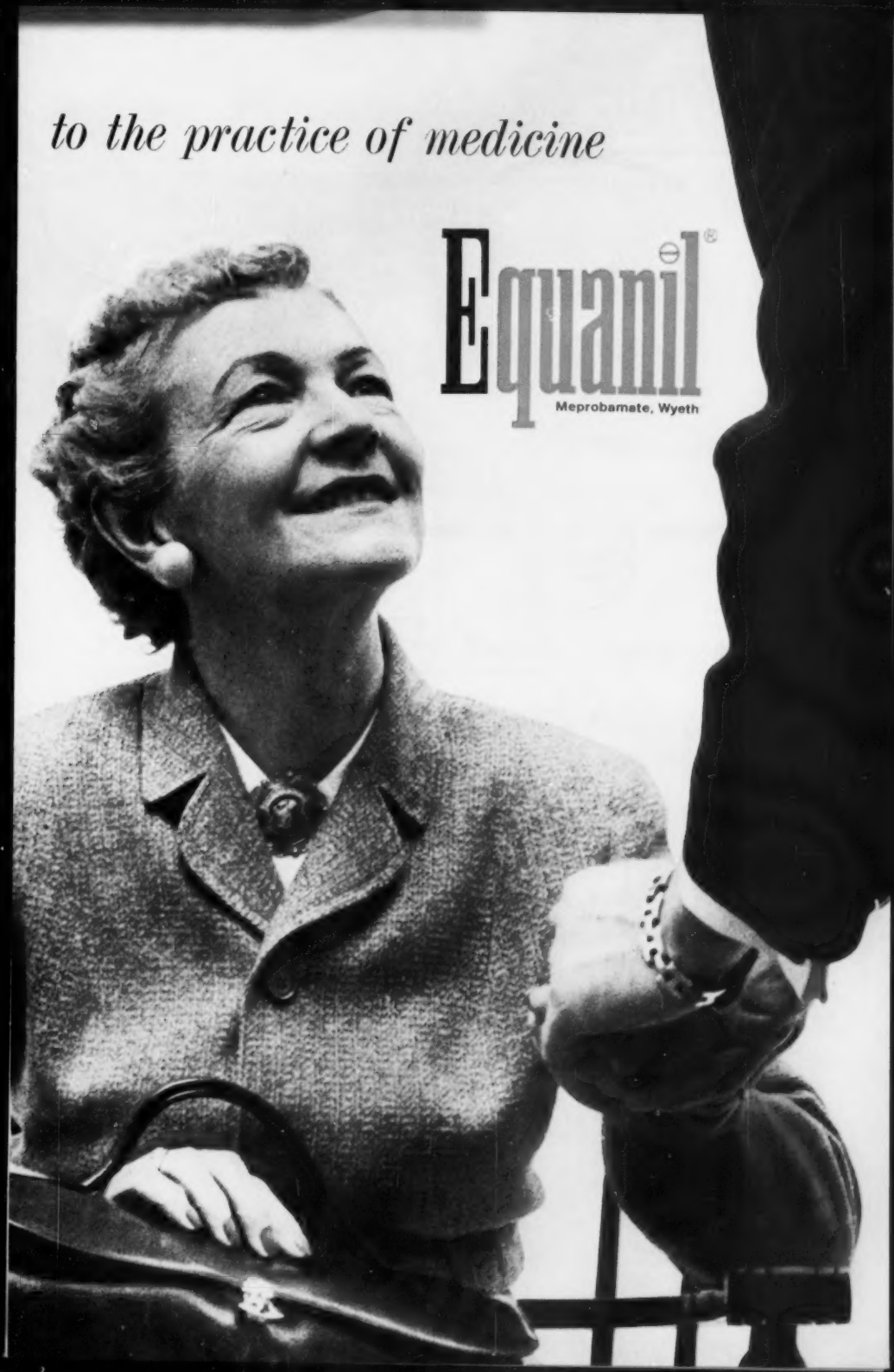

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*Wilbur, R. S., and Bolt, R. J.: Gastroenterology 38:251, 1960.

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Category	Number	Average Age, years
Normal cholecystogram	1051	46.26
Postcholecystectomy	25	51
Faint visualization	45	50.6
Nonvisualization	20	51.6
Biliary calculi	92	48.3
Total abnormal	182	49.9

*Adapted from Wilbur, R. S., and Bolt, R. J.

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1. Nesselrod, J. P.: Clinical Proctology, ed. 2, Philadelphia, Saunders, 1957. 2. Page, S. G., Jr., et al.: J. A. M. A. 157:1208, Apr. 2, 1955. 3. Gross, J. M.: J. Internat. Coll. Surgeons 23:34, Jan., 1955. 4. Page, S. G., Jr., et al.: Gastroenterology 32:747, Apr., 1957. 5. Hellman, L. D.: To be published.

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The higher dosages of "MUREL" are recommended in early therapy and in G.U. and biliary tract spasm.

1. Peiser, U.: Med. Klin. **50**:1479 (Sept. 2) 1955. 2. Berndt, R.: Arzneimittel-Forsch. **5**:711 (Dec.) 1955. 3. Rostalski, M.: Zentralbl. Gynäk. **78**:1153 (July 21) 1956. 4. Holbrook, A. A.: Am. Pract. & Digest Treat. **10**:842 (May) 1959.

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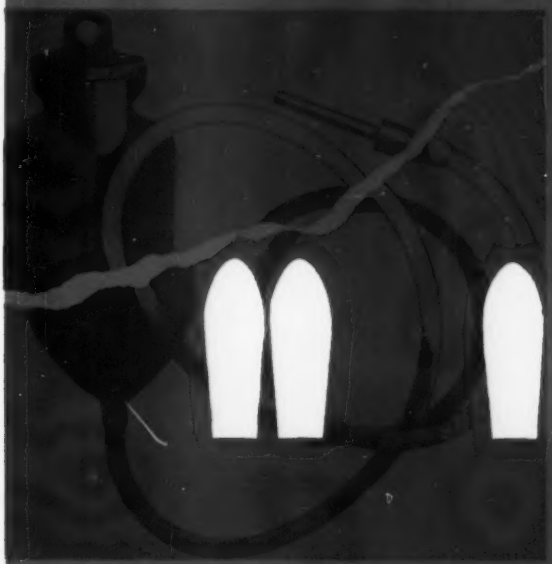

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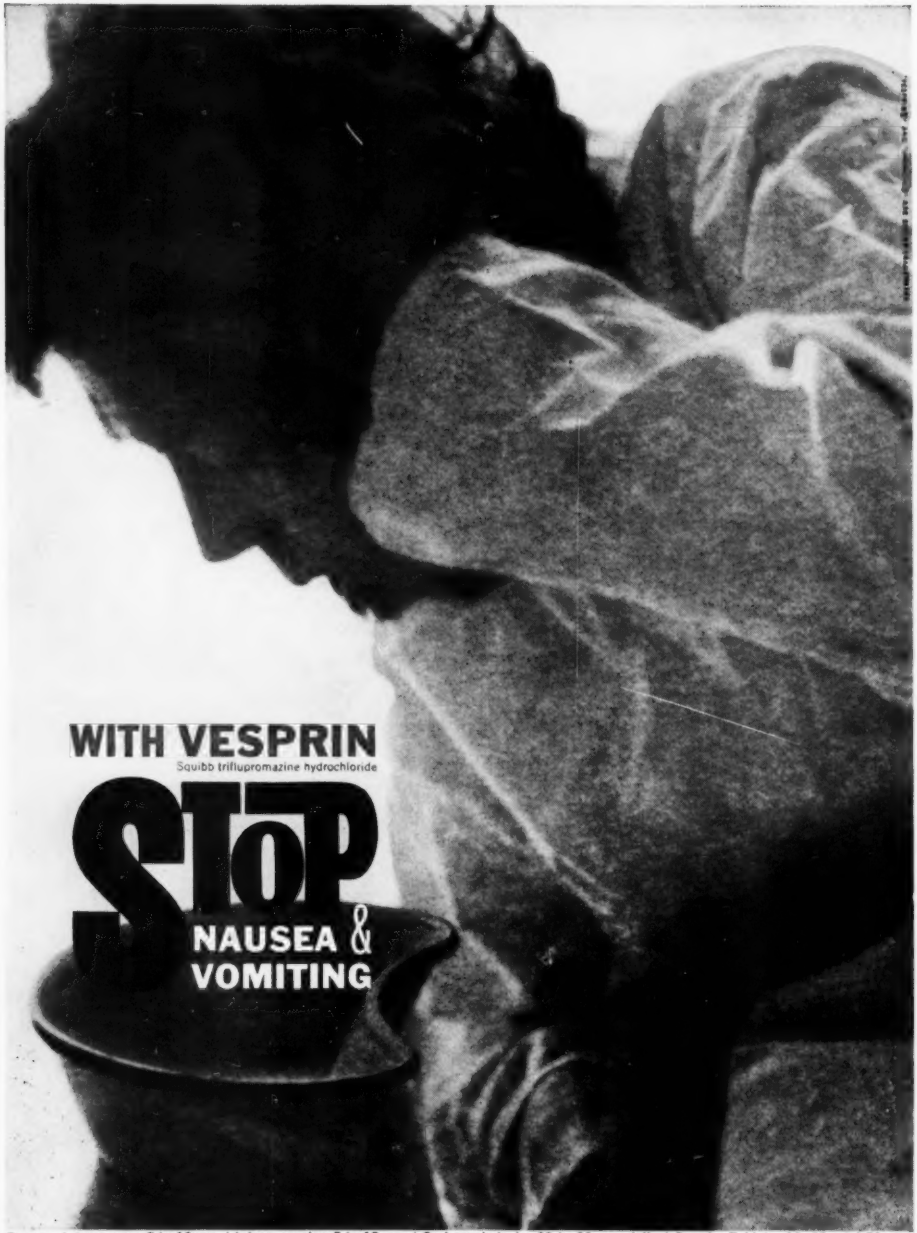

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2. Rinehart, R.E., and Marcus, H.: Incidence of Amebiasis in Healthy Individuals, Clinic Patients and Those with Rheumatoid Arthritis, Northwest Med., *54*:708 (July, 1955).

3. Webster, B.H.: Amebiasis, a Disease of Multiple Manifestations, Am. Pract. and Dig. of Treat. *9*:897 (June, 1958).

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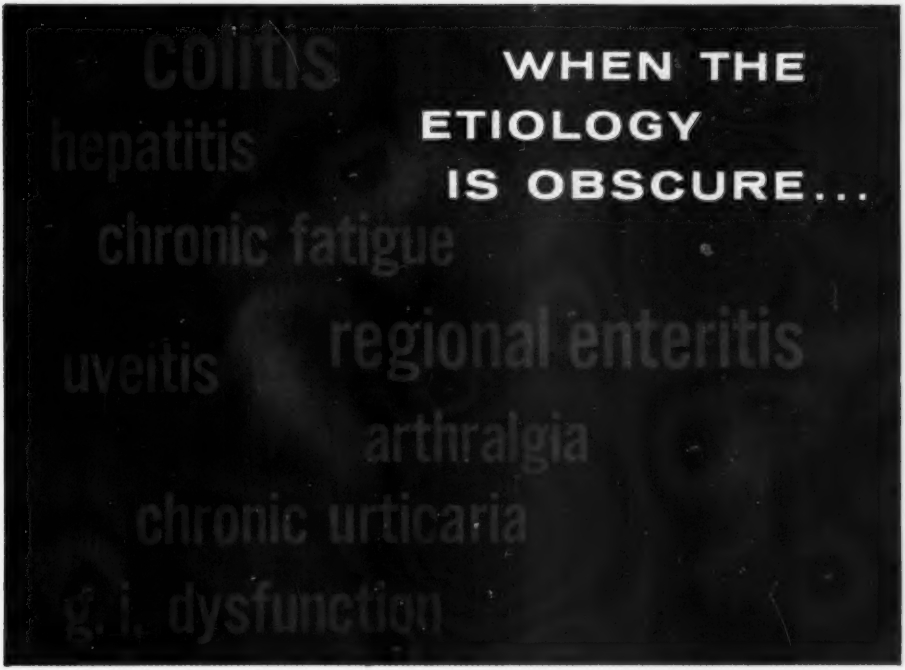

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1. Webster, B.H.: Am. Pract. and Dig. of Treat., *9*:897 (June, 1958). • 2. D'Antoni, J.S.: Am. J. Trop. Med. and Hyg., *29*:269 (May, 1949). • 3. Rinehart, R.E., and Marcus, H.: Northwest Med., *54*:708 (July, 1955). • 4. Elsdon-Dew, R.: S. Afr. Med., *32*:89 (Jan., 1958). • 5. Cook, J.E., Briggs, G.W., and Hindley, F.W.: Am. Pract. and Dig. of Treat., *6*:1821 (Dec., 1955). • 6. Farfel, B.: Am. J. of Gastroenterology, *32*:620 (Nov., 1959). • 7. Eisert, J., Hannibal, J.E., and Sanders, S.L.: New Eng. J. of Med., *261*:843 (Oct. 22, 1959). • 8. McHardy, G.C.: Gastroenterology, *30*:535 (1956). • 9. Moan, J.C.: Am. J. Trop. Med. and Hyg., *6*:499 (May, 1957). • 10. Babione, R.W., and Moan, J.C.: (to be published). • 11. Babione, R.W.: (to be published). • 12. Perkins, J.G.: U. of Oregon Med. School, Mar. 19-20, 1959.

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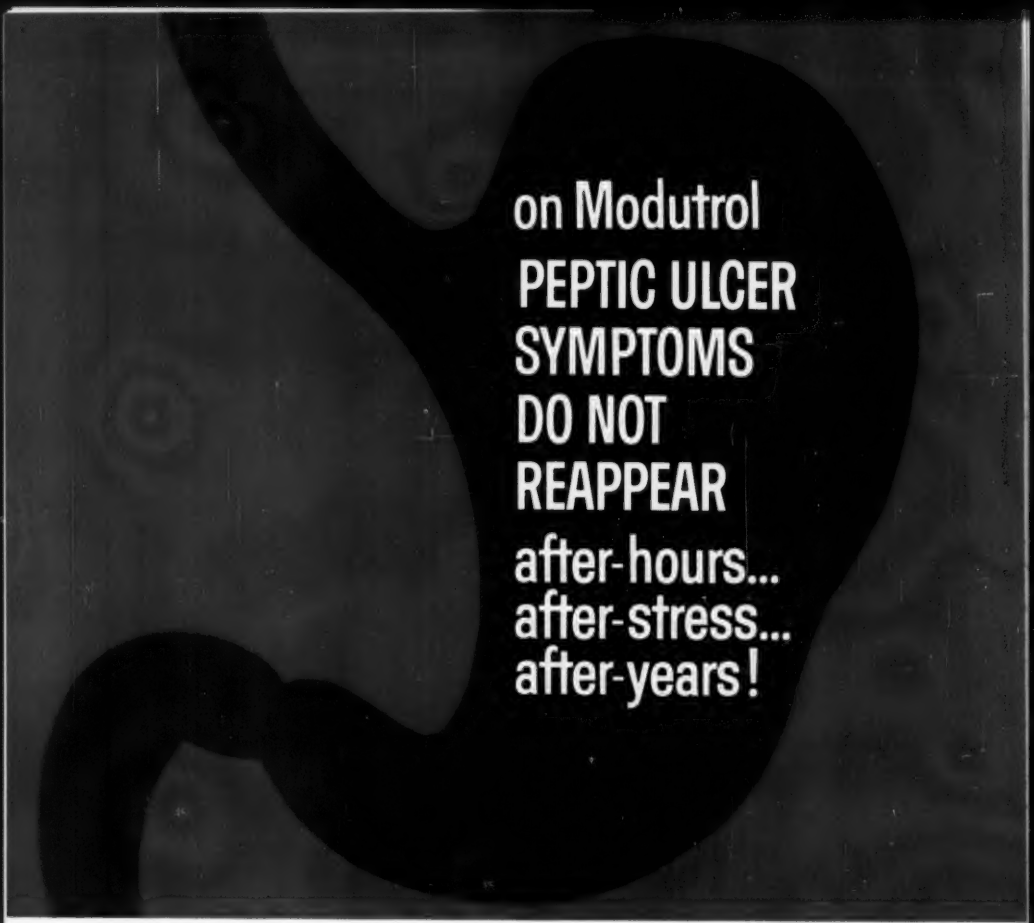

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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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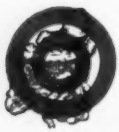

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